SUPPLEMENTAL METHODS

Data Extraction

One investigator extracted descriptive information, which was confirmed by a second investigator; discrepancies were resolved by consensus. We extracted the following information from each paper: author name and year of publication; study location and enrollment period; number of patients and participating institutions; study design; clinical context and setting; patient selection criteria; definition of FUO; details on work-up strategies before nuclear imaging; proportion of use of CT; reference standard tests; follow-up duration after imaging; characteristics of enrolled patients (e.g., mean or median age, proportion of male patients, time from the onset of symptoms to imaging, proportion of positive inflammation markers, i.e., CRP or ESR, and final diagnosis of the FUO cause); imaging preparations and protocols (1-6); and diagnostic criteria for visual and quantitative assessment.

We operationally categorized studies into three groups based on their pre-imaging diagnostic workup procedures (7): "first-level examinations" included basic laboratory tests, blood cultures, serologic and immunologic tests, chest x-ray, tests for tuberculosis and abdominal ultrasound or CT, or similar tests; "second-level examinations" included cryoglobulin measurements, chest and abdominal CT with contrast, temporal artery biopsy, echocardiography, bone marrow biopsy, and serologic testing for specific infectious diseases in addition to the "first-level examinations"; "third-level examinations" were those that included tests beyond those in the lower levels. We considered surgery, biopsy, and culture results using surgical or aspiration materials from targeted sites to be "high accuracy" reference standards; serological tests, autoimmune tests, or operational clinical diagnostic criteria such as those for non-infectious inflammatory diseases and the modified Duke Criteria for infective endocarditis to be "moderate accuracy" reference standards; and other clinical diagnosis or clinical and/or imaging follow-up methods to be "low accuracy" reference standards.

Stability Analysis for "Benign" Causes of FUO

Diagnosing "benign", spontaneously regressing causes, which may avoid unnecessary further diagnostic work-up, may not necessarily alter their therapeutic decisions or subsequent clinical outcomes. For example, viral infections presented as FUO in immunocompetent patients typically resolve spontaneously with no disease-specific treatments, and rarely lead to serious complications or mortality. However, across-study heterogeneity that precluded a uniform analysis was observed regarding how studies classified or defined, (aggressively) investigated, and reported such "benign" causes. For example, definitively diagnosed viral infections were categorized as positive disease in

some studies (because they were [specifically investigated and thus] successfully diagnosed), but as negative disease because of non-diagnosis (or simply classified so because they were even not investigated) in others. In stability analysis, to address these variations, we considered both the diagnosed "benign" causes (originally reported as either positive or negative disease) and the cases of no diagnosis (originally reported as negative disease) to be negative disease. Our operationally defined alternative criteria for positive and negative diseases are detailed in Supplemental Table 2.

Quantitative Assessment of Indirect Comparisons

We estimated relative diagnostic odds ratios (rDORs) as the measure of comparative accuracy among two alternative imaging tests by performing univariable meta-regressions. We added the type of imaging tests as a categorical predictor for the threshold and accuracy parameters in the hierarchical summary ROC model (8,9), assuming that both threshold and accuracy were associated with the type of biomarkers and that shape of the summary ROC curves and the variances of the random effects were common (10). We also performed univariable meta-regressions to assess the difference of diagnostic yield between two imaging tests. We used the type of imaging test as a study-level predictor and corresponding regression coefficients were estimated with the generalized linear mixed-effects logistic regression. In the Bayesian summary ROC meta-regressions, we adopted the informative prior distributions as Rutter and Gatsonis recommended (8) and performed sensitivity analysis for the variance of the random effects for threshold and accuracy parameters. For all analyses, we based results on three different chains and 50,000 iterations after 5,000 burn-in iterations. We considered nodes to have converged when the Brooks-Gelman-Rubin statistic was less than 1.01 (11).

SUPPLEMENTAL RESULTS

Test Characteristics

Studies of FDG-PET and FDG-PET/CT generally adopted similar PET protocols (Supplemental Table 5). Intravenous contrast material was used in 5 of 21 PET/CT studies. Emission scans were acquired from skull base to mid-thigh, except in cases when the scan area was expanded to the whole body for assessing systemic conditions (e.g., vasculitis). FDG uptake was assessed qualitatively, using consistent diagnostic criteria across studies, and quantitatively, using standard uptake values (Supplemental Table 6).

Studies of gallium scintigraphy adopted similar imaging protocols (Supplemental Table 5). When necessary, spot and/or delayed images, and SPECT of specific body parts were added to planar scintigraphy. Increased uptake of gallium-67 was qualitatively assessed (Supplemental Table 6), but few studies reported their diagnostic criteria.

Imaging protocols were also similar across studies of leukocyte scintigraphy (Supplemental Table 5). Scans were performed approximately 24 hours after injection of radiolabelled autologous white blood cells. No studies obtained SPECT images. Again, few studies reported details of the diagnostic criteria used for qualitative assessment (Supplemental Table 6).

Indirect Comparisons

In three comparative studies some individuals were tested with both imaging tests being compared (51 out of 1720 total patients [3%] for the comparison of FDG-PET vs. FDG-PET/CT; 40 out of 983 [4%] for FDG-PET vs. gallium scintigraphy; and 43 out of 703 [6%] for FDG-PET vs. leukocyte scintigraphy). Evidence from indirect comparisons of test performance suggested that FDG-PET/CT outperformed standalone FDG-PET (rDOR=3.10; CrI: 1.00–9.53), gallium scintigraphy (rDOR=5.07; CrI: 1.13–23.57), and leukocyte scintigraphy (rDOR=11.18; CrI: 1.67–90.47) (Supplemental Figure 5). There was no evidence from indirect comparisons that any one particular imaging test outperformed another among FDG-PET, gallium scintigraphy and leukocyte scintigraphy. These results were stable in sensitivity analysis except in the two comparisons: FDG-PET/CT vs. standalone FDG-PET, and FDG-PET/CT vs. gallium scintigraphy; the wider CrIs included the null value, 1.

Regarding diagnostic yield, evidence from indirect comparisons suggested that FDG-PET/CT was the most helpful imaging modality in localizing the anatomical location(s) of a source of FUO among the four tests (Supplemental Figure 6). In contrast, leukocyte scintigraphy was outperformed by the other three modalities. There was no evidence of difference between FDG-PET and gallium scintigraphy (difference in diagnostic yield -0.08; 95% CI: -0.24–0.09; P=0.40).

Excluded Studies

Studies excluded because of editorial or letter (n = 4)

- Andres E, Federici L, Imperiale A. Value of 18 FDG-PET/CT in clinical practice in patients with fever of unknown origin and unexplained prolonged inflammatory syndrome. *Eur J Radiol.* 2010;75:122.
- Bleeker-Rovers CP, Corstens FH, Van Der Meer JW, Oyen WJ. Fever of unknown origin: prospective comparison of diagnostic value of (18)F-FDG PET and (111)In-granulocyte scintigraphy. *Eur J Nucl Med Mol Imaging.* 2004;31:1342-3.
- Blockmans D. (18f)fluoro-deoxyglucose positron emission tomography in patients with fever of unknown origin. *Acta Clin Belg.* 2004;59:134-7.
- Lee JC, Redmond AM. FDG-PET for investigation of patients with fever of unknown origin. *Intern Med J.* 2012;42(12):1368.

Studies excluded because of case report (n = 2)

- Naito T, Fukuda Y, Matsumoto N, Takeda N, Dambara T, Hayashida Y. A gallium scintigraphy of fever of unknown origin. *Internal Medicine.* 2006;45:743.
- Melsom M, Nakken KF, Bugge-Asperheim B. Gallium-67 scintigraphy. A useful diagnostic aid in fever of unknown origin and simple occult malignant tumors. *Tidsskrift for den Norske Laegeforening.* 1979;99:1657-9.

Studies excluded because of review article (n = 2)

- Meller J, Becker W. [Nuclear medicine diagnosis of patients with fever of unknown origin (FUO)]. *Nuklearmedizin.* 2001;40:59-70.
- Nazar AH, Naswa N, Sharma P, et al. Spectrum of 18F-FDG PET/CT findings in patients presenting with fever of unknown origin. *Am J Roentgenol.* 2012;199:175-85.

Studies excluded because non-FUO patients are assessed (n = 6)

- Bar-Shalom R, Yefremov N, Guralnik L, et al. SPECT/CT using 67Ga and 111In-labeled leukocyte scintigraphy for diagnosis of infection. *J Nucl Med.* 2006;47:587-94.
- Fineman DS, Palestro CJ, Kim CK, et al. Detection of abnormalities in febrile AIDS patients with In-111-labeled leukocyte and Ga-67 scintigraphy. *Radiology.* 1989;170:677-80.
- Jaruskova M, Belohlavek O. Role of FDG-PET and PET/CT in the diagnosis of prolonged febrile states. *Eur J Nucl Med Mol Imaging.* 2006;33:913-8.
- Maugeri D, Santangelo A, Abbate S, et al. A new method for diagnosing fever of unknown origin (FUO) due to infection of muscular-skeletal system in elderly people: leukoscan Tc-99m labelled scintigraphy. *Eur Rev Med Pharmacol Sci.* 2001;5:123-6.
- Řehák Z, Fojtík Z, Staníček J, Bolčák K, Fryšáková L. 18F-FDG PET in the diagnosis of large vessel vasculitis. *Vnitrni Lekarstvi.* 2006;52:1037-44.
- Ryuko H, Otsuka F. Comprehensive analysis of 174 febrile patients admitted to okayama university hospital. *Acta Medica Okayama.* 2013;67:227-37.

Studies excluded for evaluating patients younger than 18 years of age (n = 4)

- Aydin F, Kin Cengiz A, Gungor F. Tc-99m labeled HMPAO white blood cell scintigraphy in pediatric patients. *Mol Imaging Radionucl Ther.* 2012;21:13-8.
- Blokhuis GJ, Bleeker-Rovers CP, Diender MG, Oyen WJG, Draaisma JMT, de Geus-Oei LF. Diagnostic value of FDG-PET/(CT) in children with fever of unknown origin and unexplained fever during immune suppression. *Eur J Nucl Med Mol Imaging.* 2014;41:1916-23.
- Buonomo C, Treves ST. Gallium scanning in children with fever of unknown origin. *Pediatr Radiol.* 1993;23:307-10.

- Jasper N, Dabritz J, Frosch M, Loeffler M, Weckesser M, Foell D. Diagnostic value of [(18)F]-FDG PET/CT in children with fever of unknown origin or unexplained signs of inflammation. *Eur J Nucl Med Mol Imaging.* 2010;37:136-45.

Studies excluded because of inclusion of patients infected with human immunodeficiency virus (n = 5)

- Buscombe JR, Miller RF, Lui D, Ell PJ. Combined 67Ga citrate and 99Tcm-human immunoglobulin imaging in human immunodeficiency virus-positive patients with fever of undetermined origin. *Nucl Med Commun.* 1991;12:583-92.
- Castaigne C, Tondeur M, De Wit S, Hildebrand M, Clumeck N, Dusart M. Clinical value of FDG-PET/CT for the diagnosis of human immunodeficiency virus-associated fever of unknown origin: A retrospective study. *Nucl Med Commun.* 2009;30:41-7.
- Del Val Gomez M, Gallardo FG, Carbo J, Cobo J, Garcia-Samaniego J. Gastroduodenal uptakes in the scans with 67Ga of the HIV infected patients studied for un-affiliated fever. *Rev Esp Med Nucl.* 1999;18:336-9.
- Martin C, Castaigne C, Tondeur M, Flamen P, De Wit S. Role and interpretation of fluorodeoxyglucose-positron emission tomography/computed tomography in HIV-infected patients with fever of unknown origin: A prospective study. *HIV Medicine.* 2013;14:455-62.
- Pereira AM, Husmann L, Sah BR, Battegay E, Franzen D. Determinants of diagnostic performance of 18F-FDG PET/CT in patients with fever of unknown origin. *Nucl Med Commun.* 2016;37:57-65.

Studies excluded because of irrelevant index test (n = 6)

- De Kleijn EMHA, Oyen WJG, Claessens RAMJ, Corstens FHM, van der Meer JWM. Utility of scintigraphic methods in patients with fever of unknown origin. *Arch Intern Med.* 1995;155:1989-94.
- de Kleijn EM, Oyen WJ, Corstens FH, van der Meer JW. Utility of indium-111-labeled polyclonal immunoglobulin G scintigraphy in fever of unknown origin. The Netherlands FUO Imaging Group. *J Nucl Med.* 1997;38:484-9.
- De Murphy CA, Gemmel F, Balter J. Clinical trial of specific imaging of infections. *Nucl Med Commun.* 2010;31:726-33.
- Gutfilen B, Lopes De Souza SA, Martins FPP, Cardoso LR, Pinheiro Pessoa MC, Fonseca LMB. Use of 99mTc-mononuclear leukocyte scintigraphy in nosocomial fever. *Acta Radiol.* 2006;47:699-704.
- Meller J, Ivancevic V, Conrad M, Gratz S, Munz DL, Becker W. Clinical value of immunoscintigraphy in patients with fever of unknown origin. *J Nucl Med.* 1998;39:1248-53.
- Zhang Q, Shan C, Wu P, Huang XE. Clinical value of dual-phase 18F-FDG SPECT with serum procalcitonin for identification of etiology in tumor patients with fever of unknown origin. *Asian Pac J Cancer Prev.* 2014;15:683-6.

Studies excluded because relevant data is not extractable (n = 5)

- Kelly MJ, Kalff V, Hicks RJ, Spicer WJ, Spelman DW. 111In-oxine labelled leukocyte scintigraphy in the detection and localization of active inflammation and sepsis. *Med J Aust.* 1990;152:352-7.
- Nakamura R, Nagamachi S, Hoshi H, et al. [67Ga-citrate scintigraphy in patients with fever of unknown origin]. *Kaku Igaku.* 1990;27:221-6.
- Syrjala MT, Valtonen V, Liewendahl K, Myllyla G. Diagnostic significance of indium-111 granulocyte scintigraphy in febrile patients. *J Nucl Med.* 1987;28:155-60.
- Tonami N, Ichiyanagi K, Matsuda H, et al. [Clinical evaluation of 67Ga-citrate scintigraphy to detect inflammatory lesions in patients with unknown fever (author's transl)]. *Kaku Igaku.*

1980;17:1221-30.
- Balink H, Veeger NJGM, Bennink RJ, et al. The predictive value of C-reactive protein and erythrocyte sedimentation rate for 18 F-FDG PET/CT outcome in patients with fever and inflammation of unknown origin. *Nucl Med Commun.* 2015;36:604-9.

Studies excluded for other reasons (n = 6)

- de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. *Medicine (Baltimore).* 1997;76:401-14.
- Ferdová E, Záhlava J, Ferda J. Fever of unknown origin, a value of hybrid 18F-FDG PET/CT imaging. *Ceska Radiologie.* 2008;62:23-33.
- Knockaert DC, Mortelmans LA, Deroo MC, Bobbaers HJ. Clinical value of gallium-67 scintigraphy in the investigation of fever or inflammation of unknown origin in the ultrasound and computed tomography era. *Acta Clin Belg.* 1989;44:91-8.
- Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. *J Am Geriatr Soc.* 1993;41:1187-92.
- Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin: Review of 45 cases and survey of the literature. *Medicine (Baltimore).* 1993;72:184-96.
- Zhao K, Dong MJ, Ruan LX, et al. [Value of 18F-FDG-PET/CT in diagnosis of classic fever of unknown origin]. *Zhejiang da xue xue bao. Yi xue ban [Journal of Zhejiang University Medical sciences]*. 2010;39:174-80.

Supplemental Figure 1. Quality Assessment of Studies of Nuclear Imaging Tests for Classic FUO.

	Risk of bias					Concerns about applicability		
Study ID	**DOMAIN 1 Patient selection**	**DOMAIN 2 Index test**	**DOMAIN 3 Referens standard**	**DOMAIN 4 Flow and timing**	**Appendix Differential verification bias**	**DOMAIN 1 Patient selection**	**DOMAIN 2 Index test**	**DOMAIN 3 Reference standard**
^{18}F-FDG-PET/CT								
Balink 2009 (12)	?	☹	☹	?	☹	?	☺	☺
Becerra Nakayo 2012 (13)	?	☹	?	?	☹	?	?	☺
Buch-Olsen 2014 (14)	?	?	?	?	☹	?	☺	☺
Crouzet 2012 (15)	?	☹	?	?	☹	☺	☺	☺
Ergul 2011 (16)	☹	☹	?	☹	☹	☺	☺	☺
Federici 2010 (17)	☹	☹	☹	☹	☹	?	☺	☺
Ferda 2010 (18)	?	?	?	?	☹	?	☺	☺
Fu 2010 (19)	?	☹	?	?	☹	☺	☺	☺
Fu 2013 (20)	?	?	?	☹	☹	☺	☺	☺
Gafter-Gvili 2014 (21)	?	☹	?	?	☹	?	☺	☺
Hamed 2014 (22)	?	☹	?	?	☹	☺	☺	☺
Kang 2015 (23)	?	☹	☹	?	☹	☺	☺	☺
Kei 2010 (24)	?	☹	☹	?	☹	☺	☺	☺
Keidar 2008 (25)	☹	☹	☹	?	☹	☺	☺	☺
Kim 2012 (26)	?	?	☹	?	☹	☺	?	☺
Manohar 2013 (27)	?	☹	☹	?	☹	?	☺	☺
Pedersen 2012 (28)	☹	?	☹	?	☹	☺	☺	☺
Pelosi2011 (29)	?	?	☹	?	☹	☺	☺	☺
Sheng 2011 (30)	?	☹	☹	?	☹	☺	☺	☺
Singh 2015 (31)	☹	?	☹	☹	☹	?	☺	☺
Tokmak 2014 (32)	?	☹	☹	?	☹	?	☺	☺
Zheng 2013 (33)	?	☹	☹	?	☹	?	?	☺
^{18}F-FDG-PET								
Bleeker-Rovers 2004 (34)	?	☹	?	?	☹	☺	☺	☺
Bleeker-Rovers 2007 (35,36)	☺	?	?	?	☹	☺	☺	☺
Blockmans 2001 (37)	☺	☹	?	?	☹	☺	☺	☺
Buysschaert 2004 (38)	☺	☹	?	?	☹	☺	☺	☺
Kjaer 2004 (39)	?	?	☹	?	☹	?	☺	☺
Kubota 2011 (40)	?	☹	☹	?	☹	?	☺	☺
Li 2006 (41)	?	☹	☹	?	☹	?	☺	☺
Lorenzen 2001 (42)	?	☹	☹	?	☹	☺	☺	☺
Robin 2014 (43)	?	?	☹	?	☹	?	?	☺
Rosenbaum 2011 (44)	?	☹	☹	?	☹	?	☺	☺
Seshadri 2012 (45)	?	☹	☹	?	☹	?	☺	☺
Gallium scintigraphy								
Habib 2004 (46)	?	?	☹	?	☹	?	☺	☺
Knockaert 1994 (47)	?	☹	☹	?	☹	☺	☺	☺
Meller 2000 (48)	?	?	☹	?	☹	?	☺	☺
Misaki 1990 (49)	?	?	☹	☹	☹	☺	☺	☺
Suga 1991 (50)	?	?	☹	☹	☹	?	☺	☺
Leukocyte scintigraphy								
Kjaer 2002 (51)	?	?	☹	?	☹	?	☺	☺
Kjaer 2004 (39)	?	?	☹	?	☹	?	☺	☺
Schmidt 1987 (52)	?	?	☹	?	☹	?	☺	☺
Seshadri 2008 (53)	?	?	☹	☹	☹	?	☺	☺
Seshadri 2012 (45)	?	☹	☹	?	☹	?	☺	☺
Uchida 1996 (54)	?	?	☹	?	☹	?	☺	☺

Key

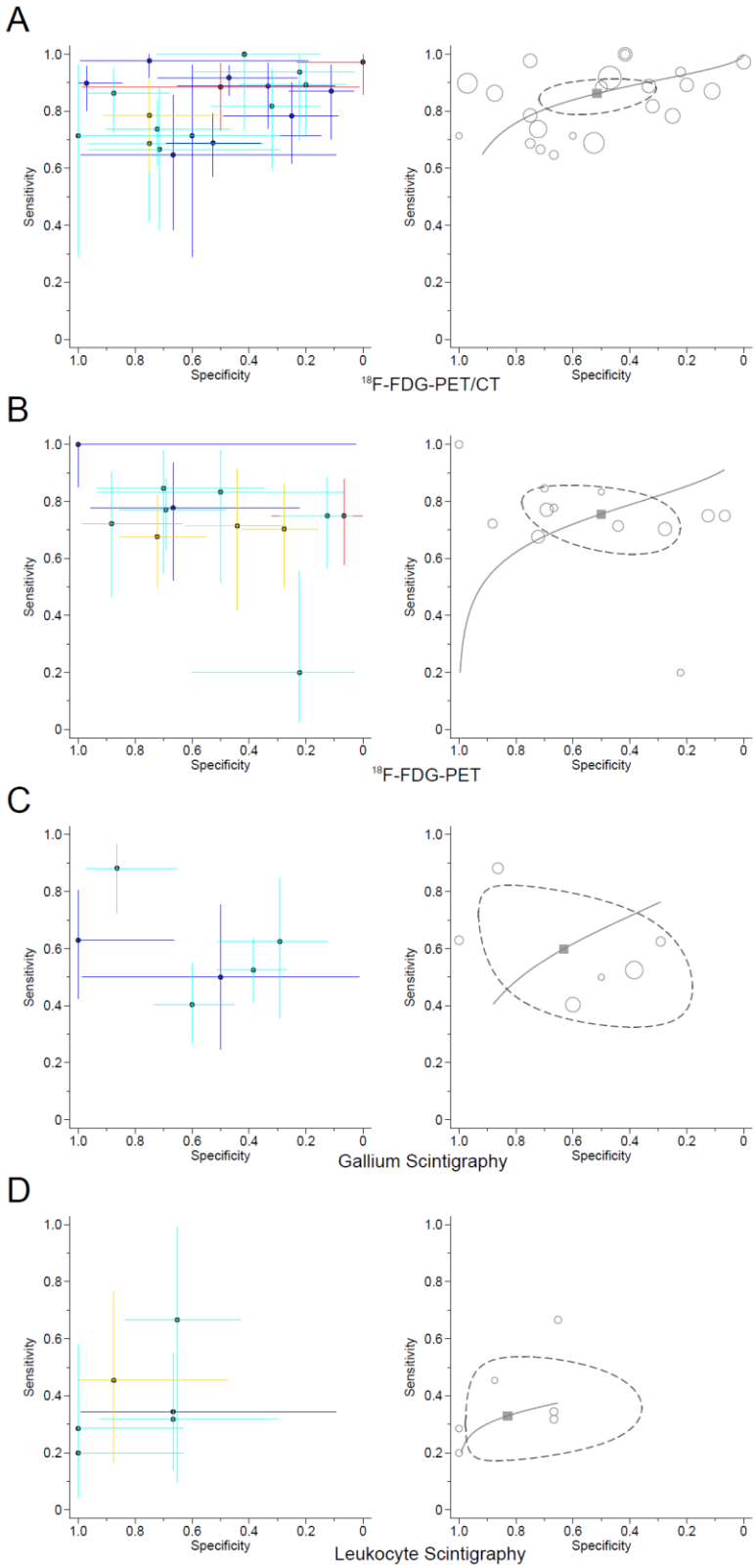
☺ Low risk of bias or concern about applicability

☹ High risk of bias or concern about applicability

? Unclear risk of bias or concern about applicability

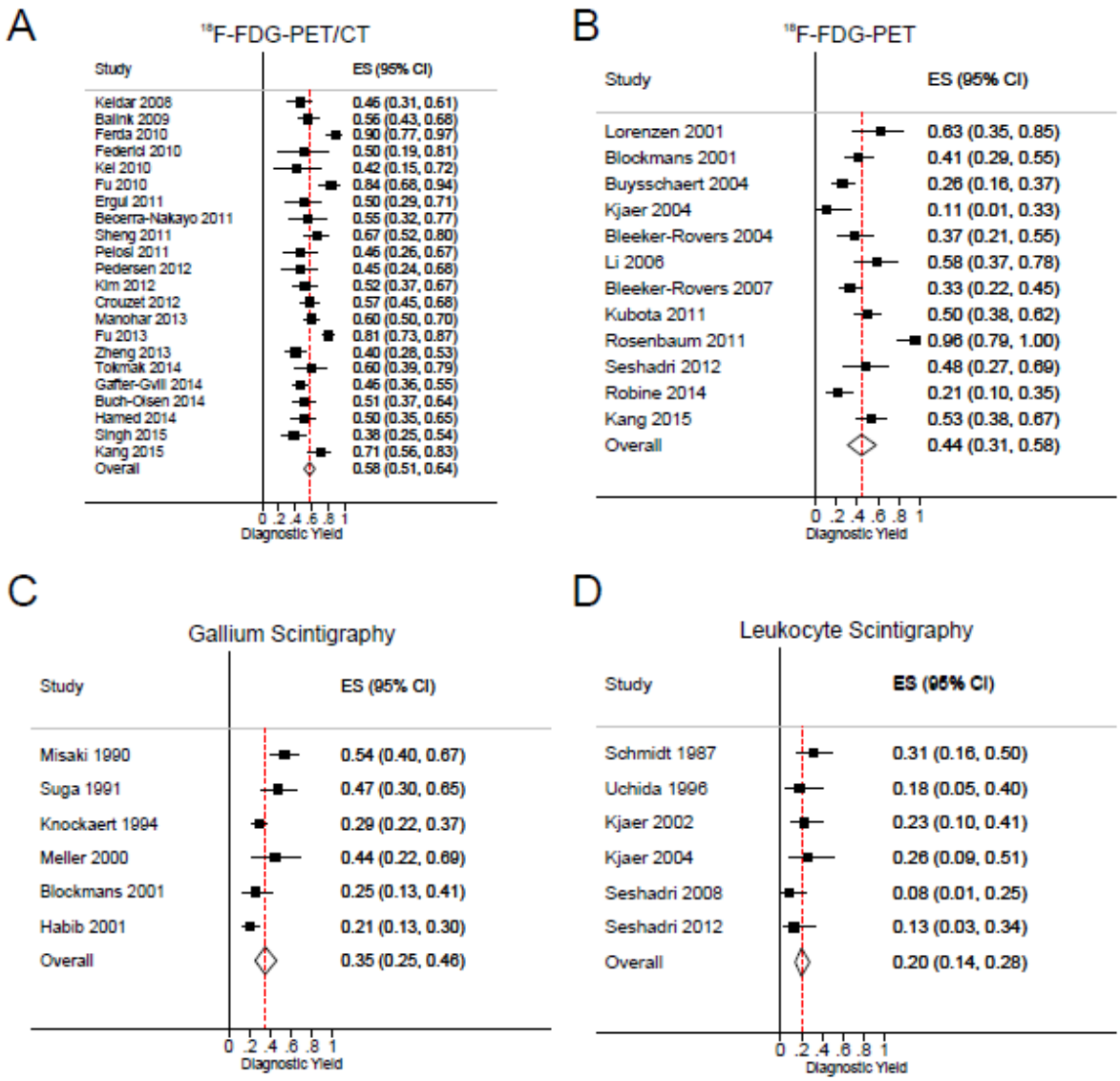
CT = computed tomography; FDG = fluorodeoxy glucose; FUO = fever of unknown origin; PET = positron emission tomography

Supplemental Figure 2. Meta-Analysis of Sensitivity and Specificity for ^{18}F-FDG-PET/CT (A), ^{18}F-FDG-PET (B), gallium scintigraphy (C), and leukocyte scintigraphy (D).



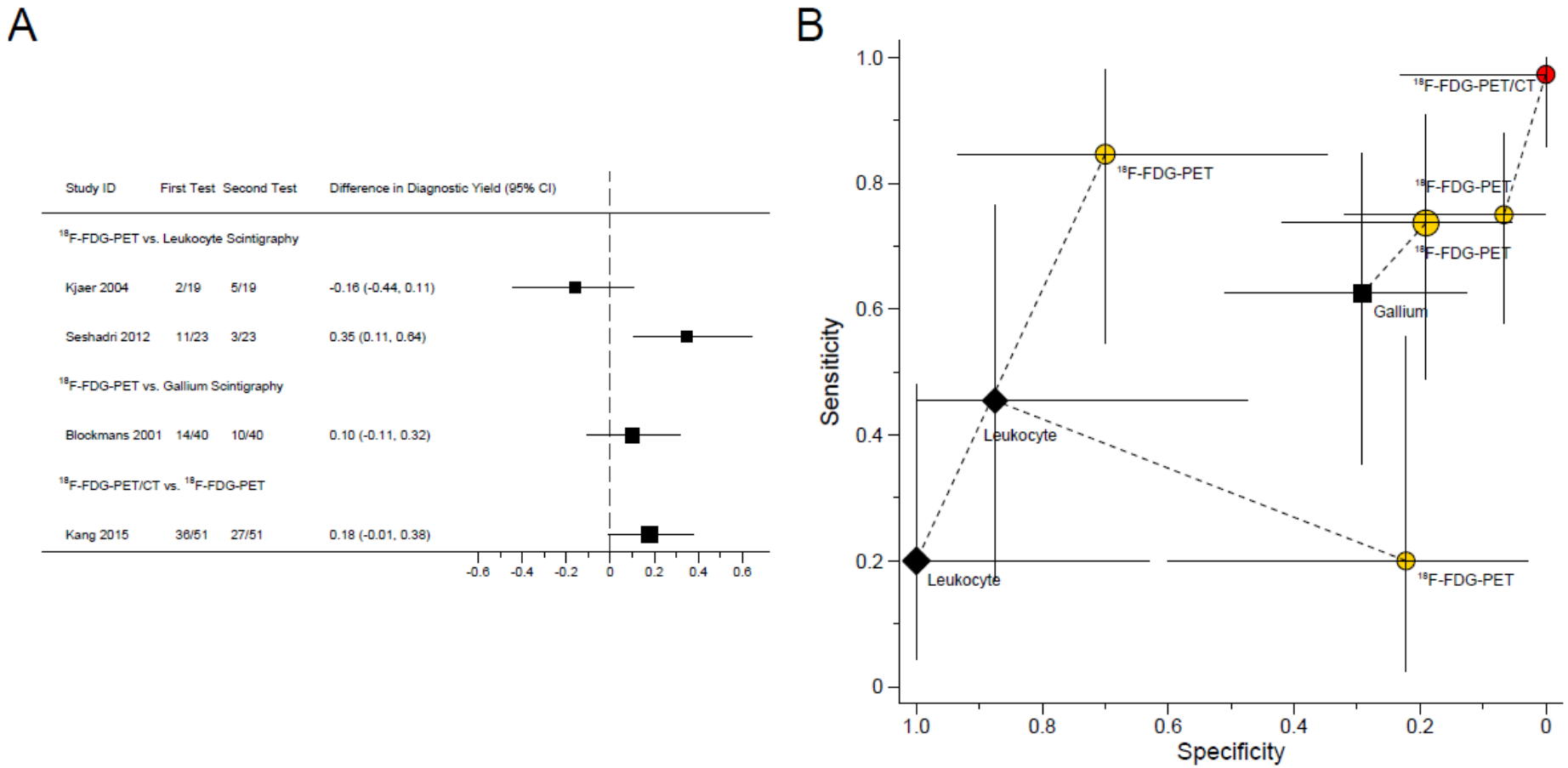
Color-coded cross-hairs receiver operating characteristics (ROC) plot (left panel) shows point estimates (shown as closed circles) and confidence intervals of sensitivity (shown as extending vertical lines) and specificity (shown as extending horizontal lines). Red, blue, cyan, and gold cross-hairs depict studies with a proportion of infections and neoplasms of >75%, 50-75%, 25-50%, and <25%, respectively. ROC plotting and hierarchical summary ROC curve (right panel) show individual study estimates of sensitivity and specificity (the size of each circle is proportional to the sample size for each study). The dashed elliptical boundary represents the 95% confidence region for the summary sensitivity and specificity (shown as the square symbol).
CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography

Supplemental Figure 3. Meta-Analysis of Diagnostic Yield for ^{18}F-FDG-PET/CT (A), ^{18}F-FDG-PET (B), gallium scintigraphy (C), and leukocyte scintigraphy (D).



The diamonds depict a summary diagnostic yield and extending lines depict 95% CIs. Each square and horizontal line indicates the diagnostic yield and corresponding 95% CI, respectively, for each study. The size of each square is proportional to the weight of each study in the meta-analysis.
CI = confidence interval; CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography

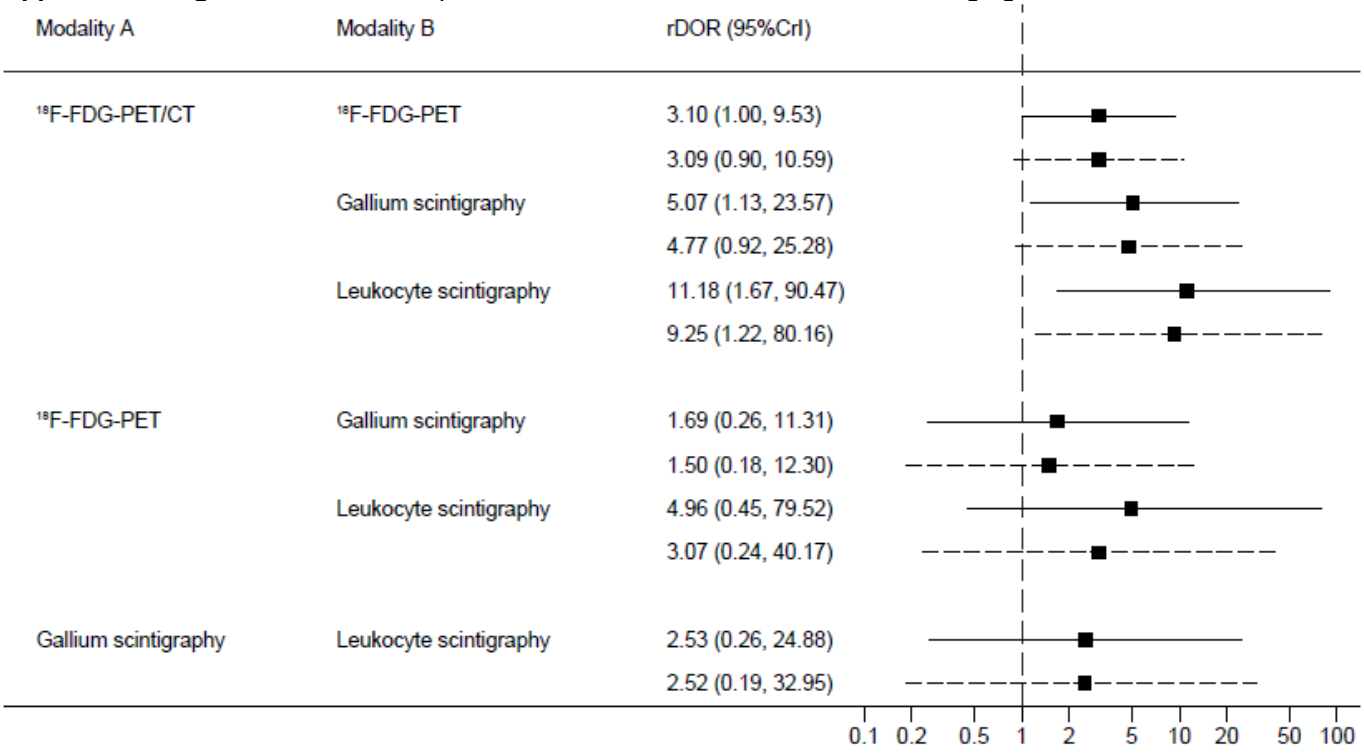
Supplemental Figure 4. Direct Comparisons of Test Performance and Diagnostic Yield of Nuclear Imaging Tests for Classic FUO.



Squares represent difference in diagnostic yield and extending lines represent the 95% confidence interval of each estimate (**A, left panel**). Crosshairs plots depict comparative accuracy estimates of competing imaging modalities and confidence intervals of sensitivity (shown as extending vertical lines) and specificity (shown as extending horizontal lines). Dashed lines connect estimates for pairs of directly compared tests. Closed square (black) and diamond (black), respectively, indicate gallium scintigraphy and leukocyte scintigraphy. Red and yellow open circles, respectively, indicate ^{18}F-FDG-PET/CT and ^{18}F-FDG-PET (**B, right panel**).

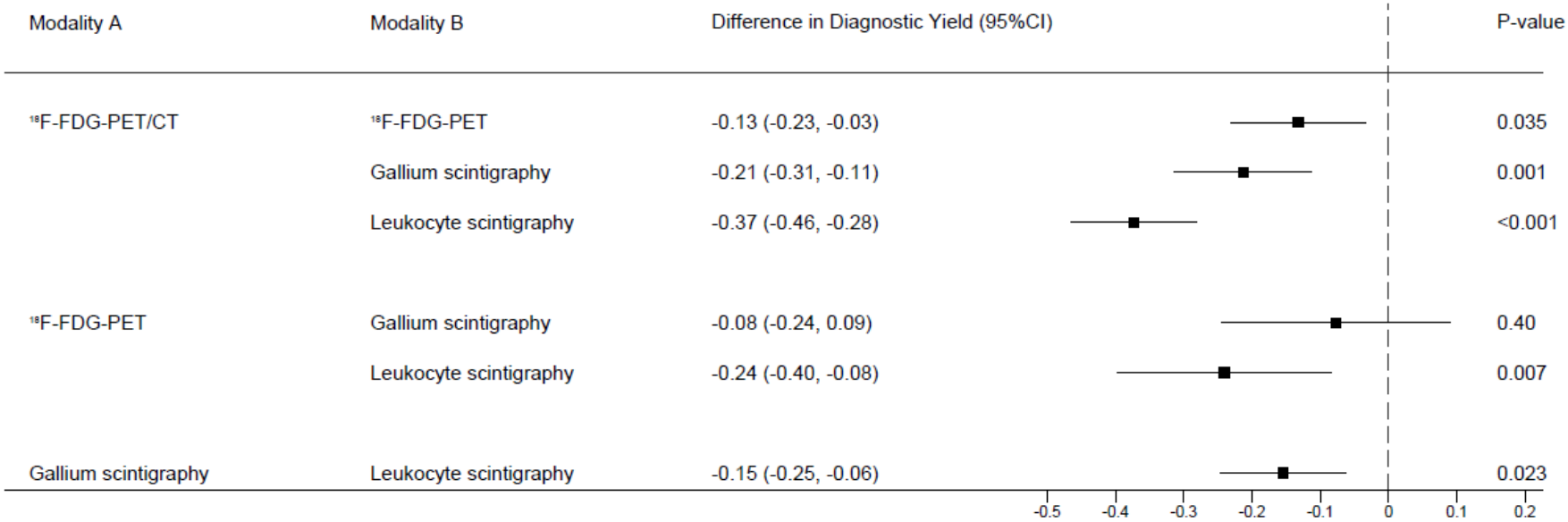
CI = confidence interval; CT = computed tomography; FDG = fluorodeoxyglucose; FUO = fever of unknown origin; Gallium = gallium scintigraphy; Leukocyte = leukocyte scintigraphy; PET = positron emission tomography

Supplemental Figure 5. Indirect Comparisons of Test Performance of Nuclear Imaging Tests for Classic FUO.



Squares represent relative diagnostic odds ratio (rDOR) between two imaging tests; extending lines represent the 95% CrI of each estimate. Solid lines are based on estimates from the main analysis and dashed lines are based on estimates from the sensitivity analysis with alternative prior distributions.
CrI = credibility interval; CT = computed tomography; FDG = fluorodeoxyglucose; FUO = fever of unknown origin; PET = positron emission tomography

Supplemental Figure 6. Indirect comparisons of Diagnostic Yield of Nuclear Imaging Tests for Classic FUO.



Squares represent difference in diagnostic yield; extending lines represent the 95% CI of each estimate.
CI = confidence interval; CT = computed tomography; FDG = fluorodeoxyglucose; FUO = fever of unknown origin; PET = positron emission tomography

Supplemental Table 1. Search strategies.

Search	Query
PubMed	
#29	Search (#28 AND #16)
#28	Search (#27 OR #10)
#27	Search (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#26	Search TA
#25	Search GCA
#24	Search temporal arteritis
#23	Search giant cell arteritis
#22	Search PMR
#21	Search polymyalgia rheumatica
#20	Search vasculitis
#19	Search bone infection
#18	Search osteomyelitis
#17	Search soft tissue infection
#16	Search (#11 OR #12 OR #13 OR #14 OR #15)
#15	Search pet/ct
#14	Search pet
#13	Search positron emission tomography
#12	Search scintigra*
#11	Search SPECT
#10	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#9	Search pyrexia of undetermined etiology
#8	Search pyrexia of undetermined origin
#7	Search pyrexia of unknown etiology
#6	Search pyrexia of unknown origin
#5	Search fever of undetermined etiology
#4	Search fever of undetermined origin
#3	Search fever of unknown etiology
#2	Search fever of unknown origin
#1	Search FUO
Scopus	
	(TITLE-ABS-KEY(fuo) OR TITLE-ABS-KEY("fever of unknown origin") OR TITLE-ABS-KEY("fever

of unknown etiology") OR TITLE-ABS-KEY("fever of undetermined origin") OR TITLE-ABS-KEY("fever of undetermined etiology") OR TITLE-ABS-KEY("pyrexia of unknown origin") OR TITLE-ABS-KEY("pyrexia of unknown etiology") OR TITLE-ABS-KEY("pyrexia of undetermined origin") OR TITLE-ABS-KEY("pyrexia of undetermined etiology") OR TITLE-ABS-KEY("Soft tissue infection") OR TITLE-ABS-KEY(osteomyelitis) OR TITLE-ABS-KEY("bone infection") OR TITLE-ABS-KEY(vasculitis) OR TITLE-ABS-KEY("polymyalgia rheumatica") OR TITLE-ABS-KEY(pmr) OR TITLE-ABS-KEY("giant cell arteritis") OR TITLE-ABS-KEY("temporal arteritis") OR TITLE-ABS-KEY(gca) OR TITLE-ABS-KEY(ta)) AND (TITLE-ABS-KEY(spect) OR TITLE-ABS-KEY(scintigra*) ORTITLE-ABS-KEY("positrone mission tomography") OR TITLE-ABS-KEY(pet) OR TITLE-ABS-KEY(pet/ct)) AND (LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "HEAL"))

Supplemental Table 2. Alternative Definition of Positive and Negative Diseases; Adapted from Varghese 2010 (7) and Cunha 2007 (55)

	Positive disease	Negative disease
Infection	Abdominal/pelvic abscess Prostatitis Chronic sinusitis Dental abscess Extrapulmonary/disseminated tuberculosis Infective endocarditis Osteoarticular/vertebral infections Typhoid/enteric fevers Endemic mycosis Brucellosis Q fever Leishmaniasis Leptospirosis Lymphogranuloma venereum Relapsing fever Relapsing mastoiditis Rat bite fever Trichinosis Malaria Rickettsial infections Whipple's disease Yersinia Cystitis Infectious disease, etiology unspecified	Epstein-Barr virus infection Cytomegalovirus infection Dengue fever Cat scratch disease/Bartonella infection Toxoplasmosis Infectious disease, spontaneous remission
Neoplasm	Lymphoma Hepatoma/liver metastasis Hepatic metastasis Renal cell carcinoma Myeloproliferative disorders/CML CLL Preleukemias/MDS/AML Colorectal cancer Pancreatic cancer Atrial myxomas Primary/metastatic CNS tumors	
Connective tissues disorder	Systemic lupus erythematosus Late onset rheumatoid arthritis Adult onset Still's disease Autoimmune hepatitis Behçet's disease Systemic vasculitis Mixed connective tissue disease Genetic autoinflammatory syndrome (e.g., familial Mediterranean fever) Polymyalgia rheumatica/temporal arteritis Periarteritis nodosa/microscopic polyangiitis Inflammatory bowel disease (Crohn/UC) Sarcoidosis Takayasu's arteritis Cryoglobulin vasculitis Cyclic neutropenia Familial Mediterranean fever Hypersensitivity pneumonitis	Kikuchi's disease Polyarticular gout Pseudogout
Miscellaneous	Deep vein thrombosis/pulmonary embolism Hypothalamic dysfunction	Drug fever (assuming any medications be discontinued)

	Protoporphyria “no identifiable specific disease”, death from disease	Alcoholic cirrhosis (assuming abstinence from alcohol) Factitious fever Hyperthyroidism Subacute thyroiditis Schnitzler syndrome Pseudolymphomas Osteochondritis dissecans Autonomic dysfunction “no identifiable specific disease” alive without specific treatments at last followup or spontaneous remission

Supplemental Table 3. Study Characteristics of Nuclear Imaging Tests for Classic FUO.

Study ID	Country, city	Role of imaging	Design	Number of centers	Patient selection	Definition of FUO	Prior tests	Use of CT as part of prior tests, %	Reference standard	Follow-up duration, *mo*	Exclusion criteria
Comparative studies											
FDG-PET vs. FDG-PET/CT											
Kang 2015 (23)	China, Beijing	2nd-level examinations	Retrospective	1	ND	Petersdorf	BLT; CXP; ECG; AUS	ND	BX; serology; immunology; microbiology; clinical diagnosis; clinical follow up	≥3	Immunocompromised patients; recent surgery; nosocomial fever
FDG-PET vs. Gallium scintigraphy											
Blockmans 2001 (37)	Belgium, Leuven	2nd-level examinations	Prospective	1	Consecutive	Durack and Street, Classic	HX; PE; BLT; CX; serology; CXP; AUS	0	ND	ND	ND
FDG-PET vs. Leukocyte scintigraphy											
Kjaer 2004 (39)	Denmark, Copenhagen	ND	Prospective	1	Inconsecutive	Petersdorf	ND	ND	BX; radiology; serology; CX; clinical follow-up	≥4	Pregnancy; lactation;
Seshadri 2012 (45)	UK, Cambridge	ND	Prospective	1	ND	Petersdorf	ND	ND	Histopathology; microbiology; serology; clinical diagnostic criteria; clinical follow-up	≥6	Immunocompromised patients; history of malignancy; recent surgery; pregnant and breast feeding women
Non-comparative studies											
FDG-PET/CT											
Balink 2009 (12)	Netherlands, Leeuwarden	ND	Retrospective	1	ND	ND	ND	ND	BX; surgery; CX; serology; and clinical follow-up	≤24	HIV/AIDS; recent surgery
Becerra Nakayo 2012 (13)	Spain, ND	ND	Retrospective	1	ND	Durack and Street, Classic	ND	ND	Pathological studies; diagnostic test; and clinical follow-up	ND	ND
Buch-Olsen 2014 (14)	Denmark, Odense	ND	Retrospective	1	ND	ND	CT; MRI; US; BS; VPS; radiography; Other radiologic exam; endoscopy; UCG; others*	19 (abdomen); 19 (chest); 10 (head)	ND	ND	ND
Crouzet 2012 (15)	France, Nimes	2nd-level examinations	Retrospective	1	ND	Durack and Street, Classic	HX; PE; BLT; BCX; UCX; SPEP; ANA; RF; TST; CXP; AUS	0	ND	≥12	Nosocomial fever; HIV infection; neutropenia; hypogammaglobulinemia; use of steroids or immunosuppressive agents for ≥2 weeks

Study ID	Country, city	Role of imaging	Design	Number of centers	Patient selection	Definition of FUO	Prior tests	Use of CT as part of prior tests, %	Reference standard	Follow-up duration, *mo*	Exclusion criteria
Ergűl 2011 (16)	Turkey, Istanbul	>2nd-level examinations	Retrospective	1	Inconsecutive	Petersdorf	BLT; BCX; CXP; body CT; abdominal MRI; scintigraphy	65 (abdomen); 80 (chest)	Imaging; BX; other invasive procedures; clinical observation	3	No adequate clinical information
Federici 2010 (17)	France, Strasbourg	ND	Retrospective	1	Inconsecutive	Fever of >38.3 Celcius for >3 weeks undiagnosed after 1 week of investigations in the hospital or in the outpatient department	BLT; BCX; UCX; tuberculosis tests (TST or sputum or urine analysis); CXP; AUS; CT†	ND†	Existing diagnostic criteria in the case of NIID	ND	Immunocompromised patient; insufficient clinical data
Ferda 2010 (18)	Czech, Plzen	ND	Retrospective	1	ND	ND	ND	ND	BX; surgery; immunology; CX; autopsy; PCR	≥6	ND
Fu 2010 (19)	China, Guangzhou	2nd-level examinations	Retrospective	1	ND	Petersdorf	HX; BLT; "routine imaging tests"	ND	Surgery; BX, clinical diagnosis, clinical follow-up	≥6	ND
Fu 2013 (20)	China, Tianjin	2nd- and higher-level examinations	Retrospective	1	ND	Petersdorf	BLT; stool test; ANA; ANCA; tumor markers; CX; CT‡; US‡; MRI‡; bronchoscopy‡; gastroscopy‡; colonoscopy‡; cytology‡	ND	Microbiology; pathology; imaging diagnosis; clinical diagnosis	≥6	ND
Gafter-Gvili 2014 (21)	Israel, Petah Tikva	ND	Retrospective	1	ND	Durack and Street, Classic; or Petersdorf	BLT; BCX; serology; CXP; US‡; CT‡; UCG‡§	54	Clinical diagnosis; microbiology; Radiology; pathology	≥6	Nosocomial fever; HIV infection; neutropenia
Hamed 2014 (22)	Egypt, Cairo	>2nd-level examinations	Retrospective	1	ND	Fever of >38.3ºC persisting without diagnosis for at least 3 weeks and undiagnosed within 1 week of clinical investigation	BLT; BCX; CXP; US; CT; MRI; bone scan; CT angiography; endoscopy	65 (abdomen); 42 (chest); 8 (Abdominopelvic); 2 (others)	ND	ND	ND
Kei 2010 (24)	Singapore	2nd-level examinations	Retrospective	ND	ND	Fever of >38.3 Celcius for >3 weeks undiagnosed in ≥3 days of in-patient or ≥2 weeks of out-patient investigation	BLT; conventional imaging tests	17	CX; BX; surgery; clinical follow-up	ND	ND
Keidar 2008 (25)	Israel, Haifa	1st-level examinations	Prospective	1	Consecutive	Petersdorf	HX; PE; BLT; BCX; UCX; CXP; AUS or abdominal CT‖	ND	Histopathology; microbiology; clinical and imaging follow-up	12-36 in case of no diagnosis	Active malignancy; recent surgery; immunocompromised patients; HIV infection
Kim 2012 (26)	Korea, Seoul	2nd-level	Retrospective	1	ND	Durack and Street,	HX; PE; BLT; BCX;	ND	Radiology; serology;	ND	Neutropenia; HIV

Study ID	Country, city	Role of imaging	Design	Number of centers	Patient selection	Definition of FUO	Prior tests	Use of CT as part of prior tests, %	Reference standard	Follow-up duration, *mo*	Exclusion criteria
		examinations				Classic	UCX; complement; ANA; CXP; AUS or abdominal CT		microbiology; pathology		infection
Manohar 2013 (27)	India, Chandigarh	Replacement for anatomical imaging	Retrospective	1	ND	Petersdorf	CXP; UCX; BCX; ANA; RF; ESR; blood smear for malaria; brucellosis serology; CECT¶; AUS¶; MRI¶	93¶	Clinical criteria for NIID; BX or fine-needle aspiration; CX; quantitative viral assay; drainage of abscess; imaging and clinical follow-up	≥6	ND
Pedersen 2012 (28)	Denmark, Copenhagen	ND	Retrospective	Multiple	Inconsecutive	Durack and Street, Classic	ND	ND	BX; serology; PET/CT; diagnostic criteria; autopsy; clinical follow-up	Mean 30 (IQR, 17–43)	Nosocomial fever; neutropenia; HIV infection; undiagnosed cases.
Pelosi2011 (29)	Italy, Torino	2nd-level examinations	Retrospective	1	ND	Fever of >38 Celcius for >3 weeks undiagnosed after CXP or chest CT, AUS or abdominal CT, BLT, and in-depth examination of any abnormalities	CXP or chest CT, AUS or abdominal CT, BLT, and in-depth examination of any abnormalities	ND	BX; surgery; clinical follow-up	Mean18 (range, 7-35)	Nosocomial fever; neutropenia; HIV infection
Sheng 2011 (30)	China, Hangzhou	>2nd-level examinations	Retrospective	1	Consecutive	Durack and Street, Classic	HX; PE; BLT; stool test; BCX; UCX; throat and sputum CX RF; ASO; TST, CXP, AUS; PET or SPECT	ND**	BX; surgery; serology; immunology; CX; clinical follow-up	≥4 in case of no diagnosis	ND
Singh 2015 (31)	India, New Delhi	>2nd-level examinations	Prospective	1	ND	Petersdorf	HX; PE; BLT; BCX; UCX; body fluid analysis; CXP; AUS; CECT; BX; bone marrow examination; tumor markers; thyroid function tests; UCG	100 (chest and abdomen)	BX; clinical diagnostic criteria; response to treatment; PET/CT	ND	Neutropenia; nosocomial fever; HIV infection; malignancy on chemotherapy; pregnant and lactating females
Tokmak 2014 (32)	Turkey, Istanbul	ND	Retrospective	1	ND	Petersdorf	ND††	ND	Histopathology; microbiology; serology; clinical follow-up	12	Active malignancy; neutropenia; nosocomial fever
Zheng 2013 (33)	China	ND	Retrospective	1	ND	Petersdorf	ND	ND	ND	ND	Nosocomial fever; immunocompromised patients; HIV infection
FDG-PET											
Bleeker-Rovers 2004 (34)	Netherlands, Nijmegen	2nd- or higher-level examinati	Retrospective	1	ND	Petersdorf	BLT, BCX, serology, CXP, AUS	86 (abdomen); 46 (chest); 14 (head)	A "three-level" diagnostic algorithm‡‡	≥6 for negative PET	Insufficient follow-up data

Study ID	Country, city	Role of imaging	Design	Number of centers	Patient selection	Definition of FUO	Prior tests	Use of CT as part of prior tests, %	Reference standard	Follow-up duration, *mo*	Exclusion criteria
		ons									
Bleeker-Rovers 2007 (35,36)	Netherlands, Nijmegen	2nd-level examinations	Prospective	6	Consecutive	Bleeker-Rovers and van der Meer§§	"Obligatory" tests for all, and specific "2nd-level" tests if PDCs identified‡‡. Cryoglobulin if undiagnostic after "obligatory" or "2nd-level" tests.	82 (abdomen); 63 (chest)	BX; serology; CX; clinical diagnostic criteria; radiology; and clinical course	Median 10 (range, 4-22) for positive PET; ≥3 for negative PET	Neutropenia; HIV infection; hypogammaglobulinemia; use of ≥10 mg prednisone or equivalent for ≥2 weeks in the previous 3 months
Buysschaert 2004 (38)	Belgium, Louvain	2nd-level examinations	Prospective	1	Consecutive	Durack and Street, Classic	HX; PE; BLT; CX; CXP; AUS	0	ND	Median 18 (IQR, 10-24)	Nosocomial fever; HIV infection; fever in immunocompromised patients
Kubota 2011 (40)	Japan, nationwide	ND	Retrospective	6	ND	Fever of ≥38 Celcius for ≥2 weeks undiagnosed after appropriate inpatient or outpatient evaluation	BLT; CXP; AUS; CT or MRI CT/MRI	73¶¶	Pathology; microbiology; clinical follow-up	Mean 5.7	Diagnosis established before PET
Li 2006 (41)	China, Shanghai	ND	Retrospective	ND	ND	Petersdorf	ND	ND	ND	ND	ND
Lorenzen 2001 (42)	Germany, Hamburg	>2nd-level examinations	Retrospective	1	ND	ND	CRP/ESR; CXP; AUS; UCG; CT (abdomen, chest, brain); endoscopy (upper GI; colon); bronchoscopy; BX (bone marrow; liver; muscle); MRI (spine; abdomen); pyelography	56 (abdomen); 69 (chest)	Immunology; BX; PET results; clinical follow-up	≥3	ND
Robin 2014 (43)	France, Lyon	ND	Retrospective	1	ND	Durack and Street, Classic	ND	ND	All clinical data approved by the authors; clinical diagnostic criteria for NIID; clinical follow-up	Mean 28 (range 1-108)	immunosuppressive disease including HIV-infection; neutropenia; nosocomial fever; insufficient examinations
Rosenbaum 2011 (44)	USA, Philadelphia	ND	Retrospective	1	ND	Petersdorf	ND	75***	BX; CX; laboratory findings; clinical follow-up	ND	ND
Gallium scintigraphy											
Habib 2004 (46)	Israel, Haifa	ND	Retrospective	1	ND	Petersdorf	Hx; PE; BLT; serologic tests; CXP; AUS; UCG; CT§§	93§§	ND	ND	Neutropenia
Knockaert 1994 (47)	Belgium, Leuven	>2nd-level examinations	Retrospective	1	ND	Petersdorf	HX; PE; BLT; CX; serology; CXP; AUS; radiological	92 (abdomen); 44 (chest);	Radiology; endoscopy; and BX for a positive scan;	ND	ND

Study ID	Country, city	Role of imaging	Design	Number of centers	Patient selection	Definition of FUO	Prior tests	Use of CT as part of prior tests, %	Reference standard	Follow-up duration, *mo*	Exclusion criteria
							studies; CT; BX; specialist consultation	24 (others) †††	radiology; endoscopy; UCG; BX; angiography; lung function studies; bronchoscopy; bone- or thyroid scintigraphy; VPS for a negative scan		
Meller 2000 (48)	Germany, Göttingen	ND	Prospective	1	ND	Petersdorf	BLT; radiology including CT; serology; bacteriology; AUS	60	Clinical follow-up; HRCT; MRI; endoscopy; BX; surgery; autopsy; CX; serology	1-6	ND
Misaki 1990 (49)	Japan, Kyoto	1st-level examinations	Retrospective	1	Inconsecutive	Fever undiagnosed after PE, BLT, and CXP	PE; BLT; CXP	0	BX; CX; laboratory findings; clinical follow-up	ND	ND
Suga 1991 (50)	Japan, Ube	ND	Retrospective	1	Inconsecutive	Fever of >37.5 Celcius for >3 weeks undiagnosed after >3 weeks of hospitalized observation	ND	ND	ND	ND	ND
Leukocyte scintigraphy											
Kjaer 2002 (51)	Denmark, Copenhagen	ND	Retrospective	1	ND	Petersdorf	ND	ND	Surgery; BX; other imaging modalities	ND	ND
Schmidt 1987 (52)	Denmark, Odense	2nd-level examinations	Retrospective	ND	ND	Petersdorf	BLT; X-ray; serology; microbiology; AUS	ND	Surgery; BX; autopsy; clinical and imaging follow-up	Median 8 (range, 2-38)‡‡‡	ND
Seshadri 2008 (53)	UK, Cambridge	ND	Retrospective	1	ND	Petersdorf	ND	ND	ND	6	ND
Uchida 1996 (54)	Japan, Chiba	2nd-level examinations	Retrospective	1	ND	Fever undiagnosed after BLT, CXP, US, and CT	BLT, CXP, US, CT	ND	CX and others	ND	ND

* Although these tests were performed before FDG-PET/CT evaluation, whether they were undiagnostic or not was not explicitly reported.

† Although 93% of the patients underwent chest and abdominal CT, it is unclear as to whether it was performed as part of prior tests.

‡ Selective patients only.

§ When these tests were performed was not explicitly reported.

|| These tests wereperformed as part of FUO workup.

¶ Although 93% of the patients underwent an anatomical imaging test (CECT, AUS, or MRI), these modalities were evaluated as comparator of FDG-PET/CT, not as part of prior tests.

** Performance of body CT (or other anatomical imaging tests) in the vast majority was inferred.

†† FDG-PET/CT was performed as part of FUO work-up in selected patients only in addition to the following tests: complete blood count, ESR, renal and hepatic function tests, electrolytes, CPK, LDH, urinalysis, CXP, AUS, Brucella serum tube agglutination, Gruber–Widal agglutination, peripheral blood smear, ANA, ANCA, RF, and BCX, UCX; cultures other than blood and urine, serologic tests for cytomegalovirus IgM, Epstein–Barr virus, Salmonella, brucella, Coxiella burnetii, Toxoplasma, rubella, herpes, and hepatitis A, B, and C viruses, UCG, CT, MRI, histopathological examination, and peripheral smear for malaria

‡‡ First-level diagnostic tests (for all patients): routine laboratory tests, blood cultures, serology, chest radiography and abdominal ultrasound; second-level tests:CT, MRI, endoscopy, biopsy, gallium-67 citrate, indium-111 labelled leucocyte or 111In-human immunoglobulin G scintigraphy, or FDG-PET (for most cases referred patients from other centers); third-level tests (selected patients only): other additional diagnostic tests, FDG-PET (selected patients for whom FDG-PET was not performed as part of the second-level tests)

§§The recently proposed criteria for classic FUO by Bleeker-Rovers and van der Meer: >38.3°C for over 3 weeks on at least two occasions, and uncertain diagnosis after history taking, physical examination, and obligatory investigations.

|||| Obligatory tests denote erythrocyte sedimentation rate or C-reactive protein, haemoglobin, platelet count, white blood cell count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase,

ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures, urine culture, chest X-ray, abdominal ultrasonography or CT, and tuberculin skin test. Second-level tests denote bone marrow biopsy, temporal artery biopsy (only those >55 years), fundoscopy, chest and abdominal CT

¶¶ Either CT or MRI; scanned anatomical regions not specified.

*** Although 75% of the patients underwent CT (chest, abdomen, and pelvis), it is unclear as to whether it was performed as part of prior tests.

††† These percentages may not necessarily be those of only CTs performed prior to the index functional imaging test.

‡‡‡ For patients with negative scintigram and without sourses of infection

AbdCT = abdominal computed tomography; AIDS = acquired immunodeficiency syndrome; ANA = antinuclear antigen; AUS = abdominal ultrasound; BCX = blood culture; BLT = basic laboratory tests (CBC, electrolytes, BUN/creatinine, ESR/CRP, CPK, LFT, urinalysis); BS = bone scintigraphy; BUN = blood urea nitrogen; BX = biopsies; CBC = complete blood count; CECT = contrast-enhanced computed tomography; CPK = creatinine phosphokinase; CRP = C-reactive protein; CT = computed tomography; CX = culture; CXP = chest x-ray; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FDG = fludeoxyglucose; FUO = fever of unknown origin; GaS = gallium scintigraphy; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HX = history taking; IQR = interquartile range; LFT = liver function test; ND = no data; NIID = non-infectious inflammatory disease; PE = physical examination; RF = rheumatoid factor; SPEP = serum protein electrophoresis; TST = tuberculin skin test; UCG = echocardiography; UCX = urine culture; US = ultrasonography; VPS = ventilation-perfusion scintigraphy

Supplemental Table 4. Patient Characteristics

Study ID	Patient, n	Duration of Sx, *weeks*	Mean/median age (range)	Male, %	Positive CRP/ESR, %	Final diagnosis (%)				
						Infection	NIID	Neoplasm	Miscellanious	No diagnosis
Comparative studies										
FDG-PET vs. FDG-PET/CT										
Kang 2015 (23)	51	Range, 3-16	54 (3-81)	63	ND	63	14	17	0	6
FDG-PET vs. Gallium scintigraphy										
Blockmans 2001 (37)	58	ND	ND	ND	ND	17	29	10	9	34
FDG-PET vs. Leukocyte scintigraphy										
Kjaer 2004 (39)	19	ND	49 (27-82)	63	ND	37	16	5	5	37
Seshadri 2012 (45)	23	ND	ND (33-83)	74	100	26	35	4	0	35
Non-comparative studies										
FDG-PET/CT										
Balink 2009 (12)	68	ND	ND (23-91)	49	ND	37	21	3	4	35
Becerra Nakayo 2012 (13)	20	ND	58 (20-80)	ND	ND	25	20	25	0	30
Buch-Olsen 2014 (14)	57	ND	57 (20-90)	54	ND	51	23	5	7	14
Crouzet 2012 (15)	79	ND	54 (ND)	46	100	29	25	15	8	23
Ergül 2011 (16)	24	Median 8; range, 3-48	58 (5-77)	75	ND	13	13	25	4	46
Federici 2010 (17)	10	Median 12; range, 3-24	53 (25-74)	40	100	40	30	0	0	30
Ferda 2010 (18)	48	ND	55 (15-89)	50	ND	38	27	17	10	8
Fu 2010 (19)	37	ND	ND (13-82) *	63*	ND	43	19	32	0	5
Fu 2013 (20)	162	ND	54 (16-88)	50	ND	35	29	22	5	8
Gafter-Gvili 2014 (21)	112	ND	60 (19-94)	57	ND	43	16	14	2	25
Hamed 2014 (22)	48	Mean 4.7; range, 3.6-24	48 (11-67)	63	ND	13	13	25	4	46
Kei 2010 (24)	12	ND	45 (13-75)	58	ND	33	8	17	0	42
Keidar 2008 (25)	53	ND	57 (24-88)	51	ND	17	30	6	2	45
Kim 2012 (26)	48	ND	48 (ND) †	51†	ND	27	35	13	10	15
Manohar 2013 (27)	103	ND	ND	ND	ND	32	10	22	4	33
Pedersen 2012 (28)	22	Median 6; 25^{th}–75^{th} percentile, 3-15*	52 (17-87)	50	100	5	14	40	0	40
Pelosi 2011 (29)	24	ND	57 (14-81)	33	100	21	33	13	4	29
Sheng 2011 (30)	48	ND	57 (24-82)	71	ND	31	19	25	0	25
Singh 2015 (31)	47	<24: 72%; ≥24: 28%	43 (ND)	66	81‡	19	21	11	2	47
Tokmak2014 (32)	25	ND	59 (16-88)	48	ND	32	40	12	0	16
Zheng 2013 (33)	67	ND	47 (14-86)	49	ND	31	12	30	3	24
FDG-PET										
Bleeker-Rovers 2004 (34)	35	Median 8; range, 3-672	51 (18-82)	43	ND	17	20	11	6	46
Bleeker-Rovers 2007 (35,36)	70	ND	53 (26-87)	46	84	17	23	7	3	50
Buysschaert 2004 (38)	74	Median 8; 25^{th}–75^{th}	56 (34-68)§	54	ND	15	23	5	16	40

Study ID	Patient, n	Duration of Sx, *weeks*	Mean/median age (range)	Male, %	Positive CRP/ESR, *%*	Final diagnosis (%)				
						Infection	NIID	Neoplasm	Miscellanious	No diagnosis
		percentile, 3-21								
Kubota 2011 (40)	74‖	ND	53 (ND)‖	53*	81‖	34	32	3	5	26
Li 2006 (41)	24	ND	ND (25-72)	75	ND	13	17	46	0	25
Lorenzen 2001 (42)	16	Median 7; range, 3-56	42 (17-78)	56	100	25	50	6	0	19
Robin2014 (43)	48	ND	57 (19-84)*	52 *	ND	6	31	4	2	56
Rosenbaum 2011 (44)	24	ND	50 (17-80)	67	ND	46	33	17	0	4
Gallium scintigraphy										
Habib 2004 (46)	102	Mean 33; range, 21-82	62 (18-90)	53	ND	33	10	12	7	38
Knockaert 1994 (47)	145	Mean 41	49 (ND)	ND	ND	20	23	6	20	32
Meller 2000 (48)	20	Median 6; range, 3-8	51 (18-67)	45	ND	40	25	10	15	10
Misaki 1990 (49)	56	ND	58 (9-86)	32	ND	34	7	5	14	39
Suga 1991 (50)	36	ND	ND (0-80)	58	ND	33	17	25	0	25
Leukocyte scintigraphy										
Kjaer 2002 (51)	31	ND	40 (13-17)	55	71	19	23	10	19	30
Schmidt 1987 (52)	32	Median, 7; Range, 3-104	61 (18-77)	50	ND	34	29	22	6	9
Seshadri 2008 (53)	26	ND	54 (18-86)¶	46¶	59¶	37¶	13¶	7¶	0¶	43¶
Uchida 1996 (54)	22	ND	ND	ND	ND	32	18	5	9	36

***** Total study patients including HIV-related FUO.

† Total study patients with FUO, not limited to those who underwent FDG-PET or FDG-PET/CT.

‡ Positive ESR was defined when it was more than 20mm/h.

§ 25^{th} – 75^{th} percentile

‖ HIV-related FUO excluded.

¶ Including patients who underwent surgery within 2 months prior to imaging.

AOSD = adult-onset Still's disease; FUO = fever of unknown origin; LLV = large vessel vasculitis; ML = malignant lymphoma; ND = no data; NIID = non-infectious inflammatory disease; SLE = systemic lupus erythematosus; Sx = symptom

Supplemental Table 5. Test Characteristics of Studies of Nuclear Imaging Tests for Classic FUO.

Study ID	Tracer	Type of PET scanner	Model (Make)	Fasting before FDG injection, *h* [blood sugar measurement]	Other preparation	Administered tracer activity, *MBq*	Time of scan after injection, *h*	Scan time, *min*	Attenuation correction	Image reconstruction method	Use of intravenous contrast material for FDG-PET/CT / Type of energy collimator[photopeak window, KeV] for scintigraphy	Scan area
FDG-PET/CT												
Balink 2009 (12)	FDG	PET/CT	Biograph 6 (Siemens, Knoxville, USA)	6 [measured but ND]	Bowel preparation performed	4 /kg body, maximum 333	1.5	3 each for 6-9 positions	Performed	OSEM	Performed	Subcranial to above the knees
Nakayo 2011 (13)	FDG	PET/CT	ND	ND	ND	ND	ND	ND	Performed	OSEM	ND	Skull base to upper third of the lower limbs
Buch-Olsen 2014 (14)	FDG	PET/CT	Discovery STE (GE, Milwaukee, USA)	6	ND	4 /kg	~1	2.5 each for 5-7 positions	Performed	OSEM	Not performed	70 cm (not specified)
Crouzet 2012 (15)	FDG	PET/CT	Gemini GXL (Philips, Amsterdam, Netherlands)	6 [<11 mmol/L]	ND	5 /kg	1	2 /position	Performed	LOR RAMLA	Not performed	Mid-thigh to the skull
Ergul 2011 (16)	FDG	PET/CT	Biograph (Siemens, Knoxville, USA)	≥4 [<150 mg/dL]	ND	296-703	1	3-4 each for 7-8 positions	Performed	ND	Not performed	Vertex to upper thigh. Lower extremities (upper thigh to feet) when indicated
Federici 2010 (17)	FDG	PET/CT	Discovery (GE, Milwaukee, USA)	6 [≤7.2 mmol/L]	ND	5.5 /kg	1	ND	Performed	OSEM	Not performed	ND
Ferda 2010 (18)	FDG	PET/CT	Biograph16 (Siemens, Knoxville, USA)	ND	Intake of mannitol solution	6 /kg	1	3 each for 6-7 positions	Performed	OSEM	Performed	Skull base to mid-thigh
Fu 2010 (19)	FDG	PET/CT	Discovery LS (GE, Milwaukee, USA)	≥4 [ND]	ND	5.5 /kg	1	4 /position	ND	OSEM	Not performed	Head to mid-thigh
Fu 2013 (20)	FDG	PET/CT	ND	≥6 [ND]	ND	370	1	ND	Performed	OSEM	Not performed	Skull base to the pubic symphysis
Gafter-Gvili 2014 UD10 (21)	FDG	PET/CT	Discovery STE (GE, Milwaukee, USA)	ND	Oral contrast media	370-666	ND	2-3 each for 5-6 positions	Performed	OSEM	Performed	skull base to mid-thigh
Hamed 2014 (22)	FDG	PET/CT	Ingenuity TF (Philips, Amsterdam, Netherlands)	4-6 [No high blood glucose levels]	Oral contrast media	296-444	1.5	ND	Performed	OSEM	Performed	Head to mid-thigh; lower-limb scanning when indicated
Kang 2015 (23)	FDG	PET/CT	GXL 16 (Philips, Amsterdam, Netherlands	6 [ND]	ND	3.7-5.18/kg	1-1.2	7-10 positions	Performed	ND	ND	Skull base to the mid thighs. Legs when potentially diagnostic clues suspected
Kei 2010 (24)	FDG	PET/CT	Biograph (Siemens, Knoxville, USA)	6 [ND]	ND	370–400	1-1.5	3-5 each for 5-7 positions	Performed	ND	Not performed	Vertex of the skull to the mid thighs
Keidar 2008 (25)	FDG	PET/CT	Discovery LS (GE, Milwaukee, USA)	4–6 [measured but ND]	ND	296–444	1.5	NA	Performed	OSEM	Not performed	Head to mid-thigh, lower-limb when indicated
Kim 2012 (26)	FDG	PET/CT	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Study ID	Tracer	Type of PET scanner	Model (Make)	Fasting before FDG injection, *h* [blood sugar measurement]	Other preparation	Administered tracer activity, *MBq*	Time of scan after injection, *h*	Scan time, *min*	Attenuation correction	Image reconstruction method	Use of intravenous contrast material for FDG-PET/CT / Type of energy collimator[photopeak window, KeV] for scintigraphy	Scan area
Manohar 2013 (27)	FDG	PET/CT	Discovery STE 16 (GE, Milwaukee, USA)	6 [<150 mg/dL]	ND	370–444	1	2 /position	Performed	OSEM	Not performed	Base of skull to mid-thigh
Pedersen 2012 (28)	FDG	PET/CT	ND	ND	ND	304–439	1	2-5 /position	Performed	ND	Performed	ND
Pelosi 2011 (29)	FDG	PET/CT	Discovery ST (GE, Milwaukee, USA)	≥6 [<160 mg/dL]	ND	222-370	1	3.5 each for 8-9 FOV	Performed	3-dimensional FORE Iterative reconstruction	Not performed	Proximal femur to the skull base
Sheng 2011 (30)	FDG	PET/CT	Biograph Sensation 16 (Siemens, Knoxville, USA)	6 [≤160 mg/dL]	Water hydration	5.5–7.4 /kg	1	3 /position	Performed	OSEM	Not performed	ND
Singh 2015 (31)	FDG	PET/CT	Biograph 2 (Siemens, Knoxville, USA)	4 [<150 mg/dL]	ND	370	0.75-1	ND	performed	ND	ND	ND
Tokmak 2014 (32)	FDG	PET/CT	Gemini (Philips, Amsterdam, Netherlands)	ND	NA	290–370	1	ND	Performed	ND	Not performed	Head to mid-thigh, or total body if indicated
Zheng 2013 (33)	FDG	PET/CT	Biograph Sensation 16 (Siemens, Knoxville, USA)	ND	ND	ND	ND	ND	Performed	OSEM	ND	ND
FDG-PET												
Bleeker-Rovers 2004 (34)	FDG	Standalone	ECAT-EXACT(Siemens/CTI, Knoxville, USA)	6 [ND]	Water intake and furosemide	200–220	1	10 /position	Performed/not performed	OSEM/FBP	NA	Proximal femora to skull base
Bleeker-Rovers 2007 (35,36)	FDG	Standalone	Dedicated full-ring PET scanner*	6 [ND]	Water intake and furosemide	200–220	1	10 /position	Performed	OSEM	NA	Proximal femora to skull base. Legs when potentially diagnostic clues suspected
Bloclmans 2001 (37)	FDG	Standalone	CTI-Siemens 931/08/12 (Siemens/CTI, Knoxville, USA)	>6 [ND]	ND	6.5 /kg	1	~90 /total scan	ND	ND	NA	Head, thorax, abdomen, and lower extremities
Buysschaert 2004 (38)	FDG	Standalone	ECAT 931/08/12 scanner or HR+ scanner (CTI/Siemens, Knoxville, TN, USA)	6	ND	6.5 /kg	1.5	10 /position; 90 /total scan	ND	ND	NA	Head, thorax, abdomen, and lower extremities
Kjaer 2004 (39)	FDG	Standalone	Advance (GE, Milwaukee, USA)	6 [ND]	ND	400	1	5 /position	Performed	FBP or OSEM	NA	Cranial vertex to pelvis
Kubota 2011 (40)	FDG	Standalone or PET/CT†	integrated PET/CT or the manual fusion of	≥5	Performed‡	250–370	1	Performed‡	Performed‡	Performed‡	ND	Upper thigh to the skull base or cranium

Study ID	Tracer	Type of PET scanner	Model (Make)	Fasting before FDG injection, *h* [blood sugar measurement]	Other preparation	Administered tracer activity, *MBq*	Time of scan after injection, *h*	Scan time, *min*	Attenuation correction	Image reconstruction method	Use of intravenous contrast material for FDG-PET/CT / Type of energy collimator[photopeak window, KeV] for scintigraphy	Scan area
			dedicated PET and CT images									
Li 2006 (41)	FDG	Standalone	C-PET (ADAC laboratories Milpitas, USA)	ND [<6.1 mmol/L]	ND	2.53 /kg	0.8-1	5 /5-6 position; 2 /7-8 position	Performed	ND	NA	Infraorbital region to mid-thigh
Lorenzen 2001 (42)	FDG	Standalone	ECAT EXACT 921/47 (CTI/Siemens, Knoxville, USA)	6	ND	400	1	90 /total scan	Performed	FBP	NA	Head to leg
Robine 2014 (43)	FDG	Standalone	ND	ND	ND	ND	ND	ND	ND	ND	NA	ND
Rosenbaum 2011 (44)	FDG	Standalone	ND	≥4 [<150 mg/dL]	ND	2.52 /kg	1	NA	Performed	OSEM	NA	Neck, thorax, abdomen, pelvis and upper-thigh
Seshadri 2012 (45)	FDG	standalone	Advance (GE, Milwaukee, USA)	≥4 [measured but ND]	ND	370	1	NA	Performed	ND	NA	Midbrain to mid-thigh, lower limb when indicated
Ga scintigraphy												
Habib 2004 (46)	Ga	Standalone	Varicam (Elscint, Haifa, Israel)	NA	ND	296–370	48§	ND	ND	SPECT image was obtained (FBP)	Medium energy collimator [93, 184, 300]	Whole body and tomographic image (SPECT)
Knockaert 1994 (47)	Ga	Standalone	a large-field-of-view camera (Siemens, Hoffman Estates, IL) with a medium-energy collimator (Scintiview, Siemens)	NA	Bowel preparation performed	75	72‖	6	ND	ND	Medium energy collimator [ND]	Anterior and posterior projections of the head, chest, and abdomen
Meller 2000 (48)	Ga	Coincidence camera	Prism 2000 (Marconi Medical Systems/Picker, Cleveland, USA)	NA	ND	185	48-72	25	Performed	SPECT image was obtained (ISA)	Medium energy collimator [93, 185, 296]	Cervical, thorax, abdomen and pelvis SPECT
Misaki 1990 (49)	Ga	Standalone	ZLC7500 (Siemens, Knoxville, USA) ,Pho/gamma LFOV (Searle、IL, USA)	NA	Bowel preparation performed	74	72	ND	ND	ND	Medium energy collimator [93, 184, 296]	Whole body, additional spot when necessary
Suga 1991 (50)	Ga	Standalone	GCA901 and GCA-401-5 (TOSHIBA, Tochigi, Japan)	NA	ND	111	48-72	ND	ND	ND	Medium energy collimator [93, 185, 300]	Whole body, additional spot when necessary

Study ID	Tracer	Type of PET scanner	Model (Make)	Fasting before FDG injection, *h* [blood sugar measurement]	Other preparation	Administered tracer activity, *MBq*	Time of scan after injection, *h*	Scan time, *min*	Attenuation correction	Image reconstruction method	Use of intravenous contrast material for FDG-PET/CT / Type of energy collimator[photopeak window, KeV] for scintigraphy	Scan area
Tonami 1980	Ga	Standalone	Picker IIc, GCA 401 (Toshiba, Tochigi, Japan)	NA	Bowel preparation performed	74	48§	ND	ND	ND	ND [184, 296]	ND
Leukocyte scintigraphy												
Kjaer 2002 2052 (51)	111In	Standalone	Millennium or XRT (GE, Milwaukee, USA)	NA	injected within 1 h after labeling	9-12	20-24	10	-	-	Medium energy collimator [171, 245]	Whole body
Kjaer 2004 2053 (39)	111In	Standalone	Millennium or XRT (GE, Milwaukee, USA)	NA	injected within 1 h after labeling	9-12	20-24	10	-	-	Medium energy collimator [171, 245]	Whole body
Schmidt 1987 3479 (52)	111In	Standalone	Maxi II (GE, Milwaukee, USA)	NA	ND	Median 8.93 (range, 3.89-16.6)	1, 2, 4, 12-24	30-45	-	-	ND [173, 247]	Thorax and abdomen
Seshadri 2008 3560 (53)	111In	Standalone	A dual headed gamma camera (Elscint, Haifa, Israel)	NA	injected within 2 h after labeling	16	3, 24	ND	-	-	Medium energy collimator [ND]	Whole body
Seshadri 2012 3561 (45)	111In	Standalone	A dual headed gamma camera (Elscint, Haifa, Israel)	NA	injected within 2 h after labeling	16	4, 24	ND	-	-	Medium energy collimator [ND]	Whole body
Uchida 1996 4019 (54)	111In	ND	ND	NA	injected within 15-20 min after labeling	ND	24	ND	-	-	Medium energy collimator [173, 247]	ND

***** Philips Allegro, Eindhoven, ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA.

† Advance, Discovery LS/ST (GE, Milwaukee, USA); Biograph 16 (Siemens, Knoxville, USA); Gemini (Philips, Amsterdam, Netherlands).

‡ Performed according to the guidelines by the Japanese Society of Nuclear Medicine.

§S can was repeated at 72 and 96 hours post injection if deemed necessary.

|| Abdominal imaging was repeated 12-24 hours after the initial scan if abdominal tracer was detected.

FBP = filtered backprojection; FDG = fluorodeoxyglucose; FORE = Fourier rebinning; FOV = field of view; Ga = gallium; ISA = iterative signature algorithm: NA = not applicable; ND = no data; OSEM = ordered subsets expectation maximization; PET = positron emission tomography.

Supplemental Table 6. Diagnostic Criteria and Interpreters of Nuclear Imaging Tests for Classic FUO.

Study ID	Positive criteria	Negative criteria	Number of interpreters	Interpreters [experience]	Blinding to clinical information and final diagnosis
FDG-PET/CT					
Balink 2009 (12)(1)	Any focal or diffuse FDG uptake: 1) intensity higher than that of surrounding tissues 2) localized to an area that did not correspond to the physiologic distribution in correlation with the corresponding CT slices	FDG activity in areas of the physiologic tracer distribution and no sites of increased uptake	2	NMP and radiologist [ND]	Not blinded
Nakayo 2011 (13)	At least one lesion with pathological metabolism (SUVmax >2.5), not explained by physiological uptake	No abnormalities	2	NMP [experienced]	ND
Buch-Olsen 2014 (14)	ND	ND	1	NMP [specialist]	ND
Crouzet 2012 (15)	Focal accumulation of FDG outside of physiologic uptake areas	ND	ND	ND	ND
Ergul 2011 (16)	Accumulation of FDG outside the physiological uptake, SUVmax calculated; the positive threshold not explicitly defined.	ND	1	NMP [experienced]	ND
Federici 2010 (17)	Focal accumulation of FDG outside the physiological uptake. SUV used as supplement; the positive threshold not explicitly defined.	ND	ND	ND	ND
Ferda 2010 (18)	ND	ND	ND	ND	ND
Fu 2010 (19)	*Any focal or diffuse F18-FDG uptake, with intensity higher than that of surrounding tissues, and in correlation with the corresponding CT slices, localized to an area that did not correspond to the physiologic biodistribution of the radiopharmaceutical was considered as pathologic	ND	2	NMP [experienced]	ND
Fu 2013 (20)	ND	ND	ND	ND	ND
Gafter-Gvili 2014 (21)	≥1 area of "pathological" FDG uptake.	FDG activity only in areas of the physiologic tracer distribution or no sites of increased uptake	1	NMP and radiologist [expert]	Blinded to final diagnosis
Hamed 2014 (22)	Accumulation of FDG outside the physiological uptake, SUVmax calculated; the positive threshold not explicitly defined.	ND	1	NMP and radiologist [experienced]	ND
Kang 2015 (23)	FDG uptake higher than surrounding physiological uptake (for FDG-PET) and abnormal structural change or abnormal CT density (for CT). Both criteria were used for FDG-PET/CT.	ND	2	NMP/radiologist ["highly qualified"]	Not blinded to clinical info
Kei 2010 (24)	Any FDG accumulation, which could not be explained by physiological distribution	ND	ND	ND	ND
Keidar 2008 (25)	≥1 area of increased FDG uptake with intensity higher than that of surrounding tissues	FDG activity only in areas of the physiologic tracer distribution or no sites of increased uptake	2	NMP and radiologist [ND]	Not blinded
Kim 2012 (26)	ND	ND	2	NMP [ND]	ND
Manohar 2013 (27)	Any focus of FDG uptake above the mediastinal background not compatible with physiological uptake	ND	2	NMP [ND]	ND
Pedersen 2012 (28)	ND	ND	Multiple	NMP and radiologist [ND]	ND

Pelosi 2011 (29)	ND	ND	2	NMP [7-year experience]	ND
Sheng 2011 (30)	FDG uptake with intensity higher than that of surrounding tissues in at least one area	No sites of increased FDG uptake	2	PET center staff [ND]	ND
Singh 2015 (31)	Any focal areas of increased FDG uptake other than physiological uptake	ND	1	NMP [experienced]; radiologist [experienced]	ND
Tokmak 2014 (32)	Increased focal uptake with higher intensity than the surrounding tissues, not corresponding to physiological uptake	ND	ND	ND	ND
Zheng 2013 (33)	Visual and semi-quantitative assessment using SUVmax was performed. Enlarged lymph nodes (>1cm in short diameter) and splenomegaly (>5 rib units) were assessed with CT. SUVmax of spleen and bone marrow higher than that of liver was deemed increased uptake.	ND	3	NMP [experienced]	ND
FDG-PET					
Bleeker-Rovers 2004 (34)	Focal accumulation of FDG outside of the areas of physiological uptake	ND	2	NMP [ND]	Blinded
Bleeker-Rovers 2007 (35,36)	ND	ND	2	NMP [ND]	Blinded
Bloclmans 2001 (37)	Focal accumulation of FDG outside of the areas of physiological uptake	ND	2 or 3	NMP [ND]	ND
Buysschaert 2004 (38)	Focal accumulation of FDG for which physiologic uptake does not account	ND	ND	ND	ND
Kjaer 2004 (39)	ND	ND	2	NMP [ND]	Blinded
Kubota 2011 (40)	A 4-grade scoring system: grade 0, lower than back ground (BG); grade 1, equivalent to BG; grade 2, higher than BG; grade 3, very strong. Grades 2 and 3 were considered positive.	2	NMP [experienced]	ND	
Li 2006 (41)	The accumulation which could not be explained by physiological uptake	ND	2>	NMP [ND]	ND
Lorenzen 2001 (42)	Any FDG accumulation which could not be explained by physiological uptake	ND	2	NMP [experienced]	ND
Robine 2014 (43)	ND	ND	ND	ND	ND
Rosenbaum 2011 (44)	Focal FDG uptake or gross CT lesions	ND	3	NMP [experienced]	ND
Seshadri 2012 (45)	FDG uptake with intensity higher than that of surrounding tissues, localized to an area that did not correspond to their physiologic uptake	FDG-uptake only in areas of physiological distribution, or no sites of increased uptake	Multiple	NMP [ND]	ND
Ga scintigraphy					
Habib 2001 (46)	ND	ND	ND	ND	ND
Knockaert 1994 (47)	Focal accumulation detected outside normal areas	No accumulation except at sites of physiological uptake	ND	NMP [ND]	ND
Meller 2000 (48)	ND	ND	2	NMP [ND]	Blinded
Misaki 1990 (49)	ND	ND	ND	ND	ND
Suga 1991 (50)	ND	ND	ND	ND	ND

Leukocyte scintigraphy					
Kjaer 2002 (51)	ND	ND	3	NMP [ND]	ND
Kjaer 2004 (39)	ND	ND	2	NMP (12)	ND
Schmidt 1987 (52)	ND	ND	ND	ND	ND
Seshadri 2008 (53)	ND	ND	2	NMP [experienced]	ND
Seshadri 2012 (45)	Leucocyte uptake with intensity higher than that of surrounding tissues, localized to an area that did not correspond to their physiologic uptake	Leucocyte-uptake only in areas of physiological distribution, or no sites of increased uptake	multiple	NMP [ND]	ND
Uchida 1996 (54)	ND	ND	2	Radiologist [ND]	ND

CT = computed tomography; FDG = fludeoxyglucose; ND = no data; NMP = nuclear medicine physician; PET = positron emission tomography; SUVmax = maximum standard uptake value

Supplemental Table 7. Failure Rates of Nuclear Imaging Tests for Classic FUO*

Study l7	Patient, n	Failure rates (%) Infection	NIID	Neoplasm	Miscellaneous
FDG-PET/CT					
Balink 2009 **(12)**	68	0/25 (0)	2/14 (14)	1/2 (50)	0/3 (0)
Buch-Olsen 2014 **(14)**	57	5/29 (17)	9/13 (69)	0/3 (0)	2/4 (50)
Ergül 2011 **(16)**	24	0/3 (0)	1/3 (33)	0/6 (0)	0/1 (0)
Federici 2010 **(17)**	10	0/4 (0)	2/3 (67)	No patient	No patient
Fu 2010 **(19)**	38	4/16 (25)	0/7 (0)	0/12 (0)	No patient
Fu 2013 **(20)**	162	6/49 (12)	8/41 (20)	1/31 (32)	1/7 (14)
Gafter-Gvili 2014 **(21)**	112	18/49 (37)	13/17 (76)	1/15 (7)	0/2 (0)
Hamed 2014 **(22)**	48	0/6 (0)	2/6 (33)	0/12 (0)	0/2 (0)
Kei 2010 **(24)**	12	2/4 (50)	0/1 (0)	0/2 (0)	No patient
Keidar 2008 **(25)**	53	5/14 (36)	1/11 (9)	0/3 (0)	0/1 (0)
Kim 2012 **(26)**	48	4/13 (31)	6/13 (46)	0/6 (0)	3/9 (33)
Manohar 2013 **(27)**	103	5/33 (15)	1/10 (10)	0/22 (0)	1/4 (25)
Pedersen 2012 **(28)**	22	0/1 (0)	3/9 (33)	0/3 (0)	No patient
Pelosi 2011 **(29)**	24	1/5 (20)	3/7 (43)	0/3 (0)	2/2 (100)
Sheng 2011 **(30)**	48	3/15 (20)	1/9 (11)	0/12 (0)	No patient
Singh 2015		5/9 (56)	1/10 (10)	0/5 (0)	1/1 (100)
Tokmak2014 **(32)**	25	1/8 (13)	1/10 (10)	0/3 (0)	No patient
Zheng 2013 **(33)**	67	10/21 (48)	8/8 (100)	2/20 (10)	0/2 (0)
FDG-PET					
Bleeker-Rovers 2004 **(34)**	35	2/6 (33)	2/6 (33)	0/4 (0)	1/3 (33)
Bleeker-Rovers 2007 **(35,36)**	70	1/12 (8)	9/14 (64)	0/5 (0)	0/2 (0)
Blockmans 2001 **(37)**	58	4/10 (40)	5/17 (29)	3/6 (50)	2/5 (40)
Buysschaert 2004 **(38)**	74	4/7 (57)	6/12 (50)	1/4 (25)	9/16 (56)
Kjaer 2004 **(39)**	19	6/7 (86)	3/3 (100)	0/1 (0)	1/1 (100)
Kubota 2011 **(40)**	74‡	2/25 (8)	9/24 (38)	0/2 (0)	4/4 (100)
Li 2006 **(41)**	24	0/3 (0)	4/4 (100)	0/11 (0)	No patient
Lorenzen 2001 **(42)**	16	0/4 (0)	2/8 (25)	0/1 (0)	0/3 (0)
Meller 2000 **(48)**	20	3/8 (38)	0/5 (0)	0/2 (0)	2/3 (67)
Robin2014 **(43)**	48	3/3 (100)	8/15 (53)	0/2 (0)	0/1 (0)
Rosenbaum 2011 **(44)**	24	0/11 (0)	0/8 (0)	0/4 (0)	No patient
Seshadri 2012 **(45)**	23	1/7 (0)	2/6 (33)	0/1 (0)	1/1 (100)
Gallium scintigraphy					
Habib 2004 **(46)**	102	27/34 (79)	3/10 (30)	3/21 (14)	5/7 (71)
Knockaert 1994 **(47)**	145	13/29 (45)	24/33 (72)	2/8 (25)	18/29 (62)
Meller 2000 **(48)**	18	5/8 (63)	3/5 (60)	0/1 (0)	2/3 (67)
Misaki 1990 **(49)**	56	2/19 (11)	1/4 (25)	0/3 (0)	0/8 (0)
Suga 1991 **(50)**	36	4/12 (33)	3/6 (50)	1/9 (11)	No patient
Leukocyte scintigraphy					
Kjaer 2004 **(39)**	19	4/7 (57)	3/3 (100)	0/1 (0)	0/1 (0)
Schmidt 1987 **(52)**	32	5/11 (45)	8/9 (89)	6/7 (86)	2/2 (100)
Seshadri 2012 **(45)**	23	4/7 (57)	6/6 100()	1/1 (100)	1/1 (100)
Uchida 1996 **(54)**	22	3/7 (43)	4/4 (100)	1/1 (100)	2/2 (100)

* Failure rates are color-coded as follows: 0%-20%=green; 20%-50%=yellow; 50%-100%=red.
‡ Patients with HIV-related FUO excluded.
CT = computed tomography; FDG = fludeoxyglucose; FUO = fever of unknown origin; NIID = Non-infectious inflammatory disease; PET = positron emission tomography

Supplemental Table 8. Causes of Classic FUO Not Localized by Nuclear Imaging Tests.*

Cause of FUO (Reference)	Total reported cases, *n*
FDG-PET/CT	
AOSD (17,20,25,26,28,30,31,33)	17
Tuberculosis (20,33)†	9
PMR (14,16,22)	6
"UTI" (25,27,31)	6
Typhoid fever (19,25,31)‡	6
"Pneumonia" (14,20,30)	5
PM/DM (20)	3
"Vasculitis" (20,28,29,33)	4
Unspecified "rheumatologic disease" (20,28)	3
Other causes	
Infections (14,19,20,24-27,29-32)§	25
NIIDs (12,14,20,26,27,29,32)‖	15
Neoplasms (12,20,33)¶	4
Miscellaneous (14,20,25-27,29)**	10
FDG-PET	
PMR (35,40,45)	6
AOSD (35,40,45)	4
SLE (35,40)	3
Unspecified "connective tissue disease" (39,41)	3
Other causes	
Infections (34,35,39,40)††	9
NIIDs (34,35,39-42)‡‡	14
Miscellaneous (39,40)§§	6
Gallium scintigraphy	
AOSD (50)	3
Takayasu's aortitis (48)	3
Other causes	
Infections (48-50)‖‖	12
NIIDs (49,50)¶¶	3
Neoplasms (50)***	1
Miscellaneous (48)†††	3

* Two or fewer cases were jointly listed according to the subcategories of "major" causes of classic FUO under "Other causes". No data were reported for leukocyte scintigraphy.

† All cases were reported from China.

‡ One case was reported from Israel, two cases from China, and the other three cases from India.

§ Ascariasis (n=1) (26); chronic urinary tract infection (n=1) (32); "colitis" (n=1) (26); "cystitis" (n=1) (14); cytomegalovirus infection (n=1) (25); dengue fever (n=2) (14,24); "endocarditis" (n=1) (14); erysipelas (n=1) (26); extraplumonary tuberculosis (n=3) (20); focal infection, unspecified (n=1) (20); infective endocarditis (n=1) (20); melioidosis (n=1) (24); pelvic inflammatory disease (n=2) (19); postoperative infection (n=1) (31); prolonged viral infection (n=1) (29); pseudomembranous colitis (n=1) (26); Q fever (n=1) (25); relapsed hepatitis B infection (n=1) (27); sepsis, unspecified (n=1) (19); upper respiratory tract infection (n=1) (30); and viral hepatitis (n=1) (30).

‖Allergic alveolitis (n=1) (14); ankylosing spondylitis (n=1) (26); aortitis (n=1) (14); autoimmune noninfectious condition, unspecified (n=1) (29); Behcet disease (n=1) (26); bilateral arteritis temporalis (n=1) (12); connective tissue disease, unspecified (n=1) (20); cyclic neutropenia (n=1) (14); familial Mediterranean fever (n=1) (32); giant cell arteritis (n=1) (14); polyangitis nodosa (n=1) (26); polymyositis (n=1) (14); SLE (n=1) (27); Sweet's syndrome (n=1) (12); and Wegener's granulomatosis (n=1) (14).

¶ Chronic lymphatic leukemia (n=1) (12); hematologic tumor, unspecified (n=2) (33); and lymphoma (n=1) (20).

** Aplastic anemia (n=1) (27); autonomic dysfunction (n=1) (20); autoimmune fever (n=1) (14); biliary microlithiasis (n=1) (29); drug fever (n=1) (25); hemophagocytosis (n=2) (26,29); myocardial infarction (n=1) (26); stroke (n=1) (14); and thyroiditis (n=1) (26).

†† Abdominal infection, unspecified (n=1) (39); bowel infection complicated by portal thrombus (n=1) (39); cytomegalovirus infection (n=1) (39); gastroenteritis (n=1) (39); meningitis, unspecified (n=1) (40); pyelonephritis (n=1) (35); sepsis, erythematosus, unspecified (n=1) (40); spondylitis (n=1) (40); and viral encephalitis (n=1) (34).

‡‡ Auto-immune thrombocytopenia, previous Bartonella infection (n=1) (39); collagen disease, unspecified (n=1) (41); Crohn's disease (n=1) (34); cryoglobulinaemia (n=1) (34); giant cell arteritis (n=1) (40); Henoch-Schönlein purpura (n=1) (35); gout (n=1) (39); microscopic polyangitis (n=2) (35); polyarteritis nodosa (n=2) (39) (40); rheumatic fever (n=2) (42); and vascular disease, unspecified (n=1) (41).

§§Chronic fatigue syndrome (n=2) (40); drug allergy (n=1) (40); erosive osteochondritis (n=1) (39); graft versus host disease (n=1) (40); and protoporphyria (n=1) (40).

‖‖ Adnexitis/salppingitis (n=1) (48); aseptic meningitis (n=1) (50); bacterial meningitis (n=1) (49); chronic pyelonephritis (n=1) (50); hepatitis C (n=1) (48); infection of a titanium implant (n=1) (48); liver abscess (n=1) (50); lymphadenitis (n=1) (50); papillitis, ascending cholangitis (n=1) (48); UTI (n=2) (49); and prolonged viral infection (n=1) (48).

¶¶ Polyangiitis nodosa (n=1) (49); polymyositis (n=1) (50); and vasculitis, unspecified (n=1) (50).

***Ovarian carcinoma (n=1) (50).

††† Hemangiomatosis of the liver (n=1) (48); hemolysis, pulmonary embolism (n=1) (48); and drug fever (n=1) (48).

AOSD = adult-onset Still's disease; FDG = fluorodeoxyglucose; FUO = fever of unknown etiology; NIID = non-infectious inflammatory disease; PET = positron emission tomography; PM/DM = polymyositis and dermatomyositis; PMR = polymyalgia rheumatica; SLE = systemic lupus erythematosus; UTI = urinary tract infection

Supplemental Table 9. Evidence on Patient-Level Predictors of Diagnostic or Management Decision Contributions of FDG-PET or PET/CT.*

Study ID	Outcomes	Selection of variables	Analysis	N of assessed variables	Patient characteristics											History						Vital signs and physical examinations						Laboratory and imaging tests											
					Age	Gender	Diabetes	Malignancy	CKD	Anorexia	Steroids or immunosuppressive therapy	Insulin therapy	Chemotherapy	Surgery	Transplant recipient	Episodic vs continuous fever	Duration of FUO	Weight loss	Empiric antimicrobial therapy	Localized pain	Investigation in another institution	Temperature	Lymphadenopathy	Cutaneous signs	Splenomegaly	Hepatomegaly	Heart murmur	CRP	WBC or leukocytosis	ESR	Hgb or anemia	PLT or thrombocytosis	LDH	SPEP	Liver function test	Fibrinogen	Hematuria	Proteinuria	Leukocyturia	Abnormal other imaging studies
FDG-PET/CT																																						
Crouzet 2012 **(15)**	DC	SE‡	UV; MV	25	2	3	3	3	3		3			3		3		2	1	3			1	3		3		1	3		1	3	3	2						
Kim 2012 **(26)**	DC	ND	ND	7	3																	3						3	2	3		3	3						
Singh 2015 **(31)**	DC	SE	ND	13		3				3							3	3					3		3	3			3	3	3	3			3					3
Zheng 2013 **(33)**	DC	ND	UV	7																					3			3	3	2	3		3			3				
Gafter-Gvili 2014 **(21)**	DC	SE§	UV; MV	23	3	1	3	3	3		3	3	3		3		1	3				3	3	2			3	3	3	3	3	3					3	3	3	
FDG-PET																																						
Buysschaert 2004 **(38)**	DC	ND	UV; MV	8	3	3										3	3					3						3		3	3								
Bleeker-Rovers 2007 **(35,36)**	DC	ND	UV	2												2					3																		
Kubota 2011 **(40)**	MC	ND	ND	2																								3	3										
Leukocyte scintigraphy																																						
Kelly 1990 **(56)**	DC	SE	UV	1																								2											
Kjaer 2002 **(51)**	DC	SE		2																								2	3										
Syrjala 1987 **(57)**	DC	SE		3																								2	3	3									

* Numbers in colored cells denote the type of predictive evidence provided: 1 = statistically significant by multivariate analysis; 2 = statistically significant by univariate analysis but non-significant by multivariate analysis; 3 = statistically non-significant.
† Fever that involves a fever-free interval of at least 2 weeks (Buysschaert 2003).
‡ All significant baseline characteristics were analyzed by univariate analysis.

§ Forward selection of all significant or borderline significant baseline characteristics by univariate analysis.
CKD = chronic kidney disease; CRP = C-reactive protein; CT = computed tomography; DC = diagnostic contribution; ESR = erythrocyte sedimentation rate; FDG = fludeoxyglucose; FUO = fever of unknown origin; Hgb = hemoglobin; MC = management contribution; LDH = lactate hydrogenase; MV = multivariate; PET = positron emission tomography; PLT = platelet; SE = statistical exploration not planned a priori inferred; SPEP = serum protein electrophoresis; UV = univariate; WBC = white blood cells.

Supplemental Table 10. Impact of Nuclear Imaging Tests on Management Decisions.

Study ID	Index test	Role of imaging	Impact	Results
Bleeker-Rovers 2007 (35)	FDG-PET	Second-level examinations	Diagnostic management	FDG-PET results lead to change in diagnostic procedures in 7 of 70 patients (10%), which were unnecessary (i.e., useless changes). No explicit descriptions on useful changes.
Kubota 2011 (40)	FDG-PET	ND	Therapeutic management	Therapeutic decisions were guided on the basis of PET results in 27 of 74 patients (36%).
Manohar 2013 (27)	FDG-PET/CT	Replacement for anatomical imaging	Diagnostic management	FDG-PET/CT results guided lymph-node biopsy in 4 of 103 patients (4%).
Tokmak 2014 (32)	FDG-PET/CT	ND	Diagnostic and therapeutic management	FDG-PET/CT results guided biopsy in 11 (44%) and therapeutic decisions in 3 (12%) of 25 patient.

CT = computed tomography; FDG = fludeoxyglucose; ND = no data; PET = positron emission tomography

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